Report of the Second

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Subject

Retrolental Fibroplasia

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RETROLENTAL FIBROPLASIA

Conference Held at

BELLEVUE MEDICAL CENTER
NEW YORK CITY
April 28, 1951

Under the Chairmanship of

L. EMMETT HOLT, JR., M.D.
PROFESSOR OF PEDIATRICS,
AND DIRECTOR OF THE PEDIATRIC SERVICE,
NEW YORK UNIVERSITY COLLEGE OF MEDICINE
BELLEVUE HOSPITAL, N. Y.

The purpose of these conferences is to assist in the correlation of the latest research information on specific topics of general interest to the practice of pediatrics, and to stimulate further research by the dissemination of information.

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We are indebted to JONATHAN T. LANMAN, M.D.
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MORNING SESSION

A Conference on Retrolental Fibroplasia convened at ten o'clock Saturday morning, April 28, 1951, at Bellevue Hospital, New York, New York, Dr. L. Emmet Holt, Jr., presiding.

CHAIRMAN HOLT: We have planned to take up, one after another, the different aspects of retrolental fibroplasia (hereafter referred to as RLF), beginning with the anatomy and pathology and pathogenesis, and clinical picture and ending up with the therapy and with the future possible lines of study.

I am going to start with Dr. Griffiths, who has made some studies of the anatomy of the eye, which I think will be of particular help to us pediatricians who are not too familiar with the eye.

DR. RAYMOND B. GRIFFITHS: It is fitting and pleasant today to pay tribute to Dr. Theodore L. Terry of Boston who, in 1942, first noted the correlation of retrolental opacity with prematurity of birth in infants, and who introduced the term "retrolental fibroplasia" for this condition. His clinical observations led him to assume that this retrolental opacity was the result of functional persistence of embryonic intraocular blood vessels; namely, the hyaloid artery traversing the vitreous from optic disc to lens, and the tunica vasculosa lentis, its ramifications around the lens. It seemed to him that this framework of vessels, persisting beyond the time of their normal involution in prematurely born infants, might well permit ingrowth of embryonic connective tissue to form a membrane behind the lens.

Subsequent serial ophthalmoscopic observations of the early course of events in many premature infants from birth by several different investigators, have revealed repeatedly that RLF does not seem to arise in this manner. Evidence now at hand indicates that funduscopic changes leading to RLF occur *after* involution of the hyaloid artery and tunica vasculosa lentis, and that if they are present at all, these structures appear only as rapidly fading rudiments. Furthermore, retrolental membrane formation seems to be a late stage of abnormal vascular changes occurring first in the retina, and then terminating in extensive intraocular disorganization.

It has been generally found that RLF appears most prevalently in premature infants of low birth weight (1360 grams or less) and of gestational age 6 to 7 months. Visible ophthalmoscopic findings in the fundus progressing to fibroplasia seem to occur early in the first few months of postnatal life, the period corresponding to the last trimester of pregnancy of full-term infants. It is during this time that the eye normally undergoes final stages of fetal development in utero. Incipient pathological changes in the retina in certain prematurely born infants, then, coincide with a late fetal developmental period.

Our preliminary considerations today might well begin with a brief review of the major steps in embryonic and fetal development of the human eye. My discussion is based on Dr. Ida Mann's excellent monograph, "The Development of the Human Eye", and the illustrations are from this book. Eyes first appear in the 2 to 3 week embryo as a pair of bilateral optic pits in the anterior end of the

FIGURE 1

Reconstruction of the optic cup of a 5 mm. human embryo seen from the front. The large vessel passing up behind the optic stalk and curving forwards above this is the internal carotid. Two main vessels can be seen below the cup; one, the future hyaloid artery, is already penetrating into the interior of the cup, the other is vascularizing its margin. Mann, "Development of the Human Eye." Courtesy of the Cambridge University Press.

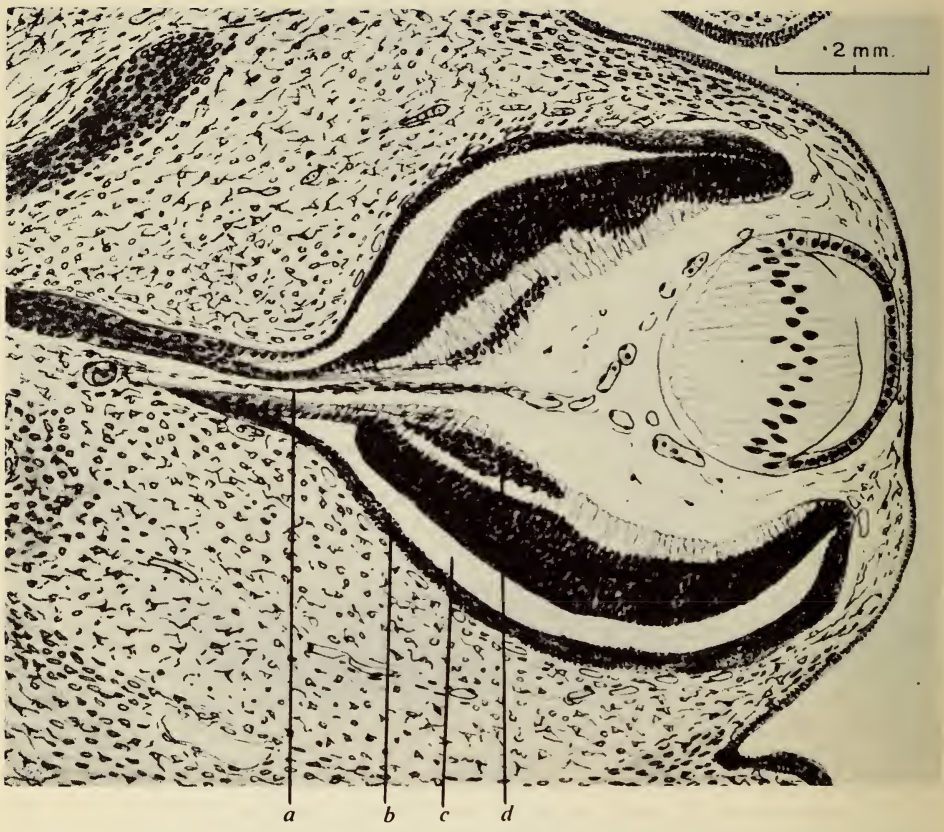

FIGURE 2

Section through the optic cup and stalk of a 17 mm. human embryo. a, hyaloid artery in upper end of fetal fissure; b, outer pigmented wall of cup; c, cavity of primary optic vesicle; d, inner layer of cup with inner neuroblastic layer. Mann, "Development of the Human Eye." Courtesy of Cambridge University Press.

open neural plate. At one month of gestation these optic pits, because of closure of the neural tube, are seen as vesicles or lateral outgrowths from the forebrain. By a process of indentation of the outer wall of the optic vesicle, this structure becomes a double-layered cup, incomplete on the ventral side where an open groove, the choroidal fissure, remains and is seen to be filled with mesoderm, later to form hyaloid artery. The lens has already made its appearance as an invagination of surface ectoderm into the rim of the optic cup. During the 6th week, closure of the choroidal fissure completes the optic cup, which now has within its interior the hyaloid artery as forward extension of the ophthalmic artery in the optic stalk. (Figs. 1 and 2). The primary vascular vitreous within the optic cup now begins to show evidence of a highly-branched hyaloid artery and its ramifications of tunica vasculosa lentis to the rapidly developing lens. At the end of 2 months gestation the intraocular hyaloid vascular system has reached its peak of development. The pupillary membrane, which is the thin mesodermal layer in contact with the outer surface of the lens, now consists of vascular arcades representing the anterior portion of the tunica vasculosa lentis.

During the 3rd month, and apparently coincident with the formation of the anterior chamber, the hyaloid system begins to undergo atrophy. By this time, the central retinal artery (from the base of the ophthalmic artery in the disc) now begins to branch upon the optic disc. During the 4th month, the tunica vasculosa lentis undergoes regression, and this process continues progressively for the remainder of gestation. By the 7th month, the hyaloid artery is considerably smaller in size, and the pupillary membrane shows atrophy in its central portion. By the 9th month, the hyaloid artery and pupillary membrane have almost disappeared. Occasionally remnants of these structures can be seen by ophthalmoscopy in the full-term infant at birth. In the premature infant the hyaloid remnant appears frequently as a small steeple-like projection from the optic disc, and the pupillary membrane still persists as fine strands across the pupil.

The process of birth at 6 or 7 months of gestation comes at a period when the eye is in an incomplete and unstable state, during which both constructive and normally retrogressive morphological activities are going on simultaneously. The background for early RLF is an immature, rapidly changing intraocular morphogenetic system, the significance of which in etiology and pathogenesis of the disease we have yet to determine.

CHAIRMAN HOLT: We will go on to the pathology. Perhaps Dr. Krause would start off.

THE PATHOLOGY OF RETROLENTAL FIBROPLASIA

DR. A. C. KRAUSE: "Retrolental fibroplasia" is a term which is not descriptive of the pathological process that occurs in this disease. It came into use when it was believed that a mass of connective tissue was formed behind the lens in association with a persistence of the tunica vasculosa lentis and the hyaloid artery. The term is unfortunately fixed in usage, so it serves now as a definitive clinical name.

The cumulative experiences of the most careful ophthalomologists who have observed the eyes of the prematures and newborn from birth to the 1st year of life indicate that the pathological process of this syndrome arises postnatally.

They have not seen this disease in the first few days of life, although the initial process may begin then. On the contrary, some ocular pathologists believe that the histologic section of some eyes of stillborn prematures have small angiomatous lesions which are suggestive of the origin of RLF. Other pathologists believe some eyes removed from older children with RLF show an abnormal persistence of the primary vitreous and angiomatous lesions of prenatal origin. At the present time the trend is toward a belief in postnatal cause of the disease.

The initial cause of the trigger mechanism is unknown in spite of the investigations of over 60 possible causes. The trend of thought is toward a postnatal metabolic disturbance. At birth in the usual early prematures the vitreous tends to be hazy, more peripherally than centrally. Remnants of the embryonic pupillary membrane, iridic arcades and pupillary structures may be present in the smallest prematures. They may persist if RLF occurs. The neonatal retinal blood vessels are small and become larger in a few weeks. The caliber of the vessels may vary quite widely in a transitory manner, wide dilatation is commonly associated with temporary peripheral haze. Neonatal hemorrhages may be absorbed so rapidly that they may not be seen a few days after birth. Severe hemorrhages are absorbed after several weeks.

The early premature neonatal peripheral retina is commonly dull to bright grey and elevated. Since this is the part of the retina that is rapidly developing, this is not surprising; for the coaptation of the anterior inner layer of the retina is still not fixed. The retina near the ora serrata may overgrow as a fold, or the outer coats may outgrow the retina leaving it temporarily as a bridge. Later the growth is compensated to give a normal eye. If this temporary physiological adjustment is too marked or too prolonged, then RLF may arise. Perhaps, this is the basis for saying that some eyes with RLF show regression. Also this temporary disturbance, if it is observed before regression, may be a factor in the report of the increased incidence of RLF. It may be said in another way; the infants who have the incipient physiologic imbalance for RLF tend to have eyes affected in this manner.

The growth of the eye is rapid after birth. The younger the infant, the more rapid is the growth. In this growing stage the vascular system of retina and choroid is more reactive than later in life. The reactive metabolic disturbances may derange the close timing of the chronological and anatomical development. If the veins become tortuous and venous dilatation marked and persistent, the vascular stasis may give rise to diffuse retinal and vitreous exudation and even hemorrhages. The exudation may occur in the retina and in the choroid, elevating the retina. In this stage the process may retrogress if mild, leaving few or no visible scars. If the process continues, endothelial and glial proliferation occurs. Connective tissue and capillary proliferation may be seen centrally or peripherally. If the connective tissue follows the space of least resistance, i.e. Cloquet's canal, a stalk or fold is formed from the disc passing forward to the lens and joining the ciliary processes. If the exudate detaches the retina with or without the aid of scar tissue in the vitreous cavity, the retina may be pushed far anteriorly toward the lens. (See Fig. 3). The retina remains attached to the optic nerve, and to the ciliary body or ora serrata. The retina becomes atrophic, gliosed and disorganized. The pull of scar tissue on the ciliary processes gives the picture of white dentations peripherally.

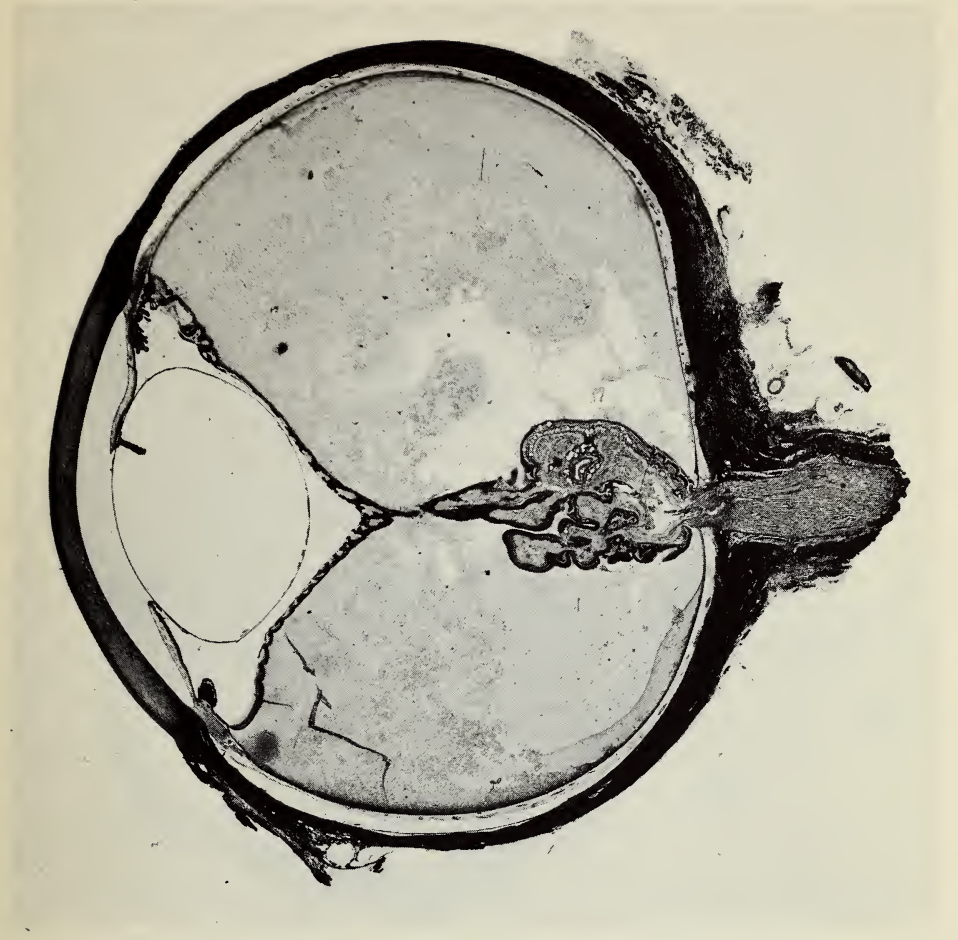

FIGURE 3

SEVERE EARLY ACUTE FORM OF RETROLENTAL FIBROPLASIA

A rapidly occurring subretinal or choroidal exudation dislocated the retina which is here represented by the irregular mass lying anterior to the optic nerve head and by the bifurcating lines passing just behind the lens to the ora serrata. A part of the ciliary body and ora serrata were detached with the retina. The part of the retina near the optic disc was a fused mass. The intraretinal space is filled with serous fluid. This detachment of the retina happened too suddenly for a marked tissue reaction. No retrolental fibroplasia (connective tissue or new vascularization) is evident. The clinical picture is a light gray red reflex in the center.

FIGURE 4

SEVERE CHRONIC FORM OF RETROLENTAL FIBROPLASIA

The retina is detached from the disc to the ciliary processes and pushed forward to the lens. It is atrophic, degenerated and cystic. The fluid behind the retina has lost its protein. The choroid is edematous. The retrolental space has a few capillaries and little connective tissue. The lens and iris fill the anterior chamber. The cornea is edematous.

This is a severe disease of long duration ending in glaucoma. Later the cornea will be opaque.

Repeated exudation and hemorrhages may occur in the residue of the detached retina, and from the choroid in the retrolental space. The lens and iris are pushed forward into the anterior chamber. The iris adheres to the lens and the lens becomes cataractous. If the iris closes the filtration angle peripherally or touches the cornea, the cornea becomes opaque.

Severe or recurrent exudation and hemorrhage or blockage of the filtration angle causes a high intraocular pressure or glaucoma. This is made noticeable by the irritability of the infant from pain and also by the redness of the eye around the cornea. Pressure atrophy finally results in a drop in intraocular pressure.

The common final result in the severe disease is a small, sightless, staring eye with a fixed, ragged, white pupil. Since the orbital contents no longer grow because of the small eye, the bulb is depressed as in endophthalmos, and the lids seemingly droop and give a false ptosis. The eyes with a retinal stalk or fold may clear except for the stalk and the retrolental mass. The stalk and connective tissue may shrink to a smaller size. The retinal vessels may be almost normal in size or distribution, or anomalous in size, position, and distribution, or absent. The retina may be moderately to extremely atrophic. The stalk may cover the macular area and thus decrease vision. This kind of eye may have poor to fair vision.

Rarely, in later childhood, the more severely scarred inner eye may have exudation and hemorrhage which destroys the residual vision. In 1 child this happened at 4 years of age.

The question arises whether or not RLF is a manifestation of a systemic disease with the pathological process visible in the eye. It is difficult to believe that it is only ocular if it arises from a metabolic, toxic, or infectious disease. A few postmortem examinations of our children with RLF have given no definite suggestions of a specific disease.

There is some evidence of systemic damage from our records obtained by following these children from birth to death by a pediatrician, neuropediatrician, child psychologist, and an ophthalmologist in a group project lasting 14 years.

We have evaluated the mental status of our RLF patients. Most of the children are tested by the same experienced child psychologist about once or twice a year. The neuropediatrician examines the child as often as necessary. The child is followed in the one school and institution. A few are above average mentally for a normal sighted child at the same age, but most infants are ordinary blind children. The retarded group is relatively large, for they are retarded by genetic and environmental factors. Our children come from white families that represent a typical cross section of northern urban communities and that attend a private clinic. Without relation to sight, the number that are defective and are dead is abnormally high in proportion to prematures without RLF. At present, 10 are dead and 10 are in institutions for the mentally handicapped. A few are in foster homes. Thirty-three infants who are less than 3 years old are difficult to classify and have a doubtful future. If the older infants with RLF are considered as a group, then the percentage of subnormal children is remarkable. The rate of mortality and the large number of children in state institutions for the mentally handicapped are much higher than they are for a corresponding number of sighted prematures of the same age group. It would seem that a general systemic disease is a part of RLF.

DR. T. H. INGALLS: Have you ever seen a completely unilateral involvement after the disease has run its course?

DR. KRAUSE: Yes, we have had several of those. In 1 you could not tell that the uninvolved eye was affected at all.

DR. WILLIAM C. OWENS: The concept of RLF has changed greatly since 1942 when it was first described by Dr. Terry. The disease, as Dr. Terry described it, was the disease as he had seen it in its late stages and was characterized by the formation of a mass of tissue behind the lens, shallowing of the anterior chamber, and arrest in growth and disorganization of the globe.

Unfortunately, in the early description, many other groups of cases presenting somewhat similar pathological changes were confused and included in the description of RLF. However, later observations have shown that a distinct clinical entity appearing in premature infants can be separated from the heterogenous group. This entity can be called RLF in premature infants. One of the 1st things we have to do is to limit ourselves to this distinct clinical entity of RLF in the premature infant.

Gradually, over a period of years, the concept of RLF in the premature infant became more clinically defined by the realization that the disease was a disease of the retina and not a disease of the hyaloid system, and that it was not related in any way to the hyaloid system.

If observations are made on premature infants at a very early period in their postnatal life, the eyes are found to be entirely normal. They differ in no respect from the eyes of premature infants who do not develop RLF, but in and about the 4th to 6th week of postnatal life, certain of these infants will develop enlarged retinal vessels. The veins become 2 to 4 times their normal size. They had previously been small, but show dilatation. Accompanying this dilatation of the veins, a marked tortuosity of the arteries, and the small branches of the veins break down into the numerous finger-like projections in the periphery. This is the 1st stage in the clinical development of RLF — the stage of change in the vessels.

From a clinical standpoint, during the 2nd stage of the acute phase the retina is involved. Here we see a clouding or graying of the retina in patchy areas which are usually located in the periphery but may be in the posterior pole. During this phase, scattered hemorrhages are found over the surface of the retina.

The 3rd stage in the acute phase is the stage in which the vitreous becomes involved. The areas of graying expand, the retina becomes elevated and finally detached; the blood vessels become more numerous and branching; and the areas of new vessel formation spread out over the surface of the retina and finally pull the retina into the disorganized mass in the vitreous.

There are several things that we have to bear in mind in talking about RLF. The 1st is that when RLF was first described, it was described in its end stages, and many other diseases which are now known not to be RLF were incorporated in that clinical description.

The 2nd point is that from this group of cases has been differentiated a group which constitute the RLF of prematurity, which is a disease of the retina

and the retinal blood vessels. It has an active course and often ends in a cicatricial form after the acute phases of the disease have subsided.

In the early study of RLF the only specimens that were available for pathological studies were the specimens removed during the late stages. These eyes were usually removed because of the diagnosis of retinoblastoma—the suspected diagnosis of retinoblastoma, as Dr. Krause has indicated. But, after the clinical course of acute RLF was recognized, everyone sat around waiting for 1 of these premature infants with the acute stage of the disease to die. Of course, the chances of obtaining such a circumstance were not very great, because if the infant survived the early initial postnatal life he usually went on growing and no specimen was obtained unless some accident supervened.

But we gradually collected about 7 specimens of early RLF and about 3 specimens of intermediate stages of RLF. These show the early pathological lesions and the changes which go on to form the end stages of the disease.

When the specimens were obtained from early stages, there were no signs of any inflammatory lesions. The choroid, iris, and retina were completely free of any type of inflammatory cells. There were no polymorphonuclear cells, no plasmacells or lymphocytes or epithelial cells. The early lesion was confined to the inner layer of the retina (the nerve fiber layer). In localized patches in the nerve fiber layer you could see small areas of proliferated endothelium. The endothelial cells showed marked growth. The endothelial cells are large cells with large, pale-staining nuceli. They were arranged in little whorls which resembled kidney glomeruli in their superficial appearance under the microscope.

Surrounding these areas of endothelial proliferation was a marked increase in the glial cells. Surprisingly enough, these growths took place without any apparent damage to the surrounding tissue. There is a supporting structure in the retina called Muller's fibers. These are easily indentifiable cells with long fibrillar processes. The capillary dilatations can be seen pushing aside the Muller's fibers which form a basket around the proliferated endothelium and there was no evidence of any death or necrosis of the retinal tissue.

In these sections we found areas of edema of the retina and small hemorrhages. Surprisingly enough, immediately beneath the nerve fiber layer, the ganglion cells and the inner plexiform layer of the retina were perfectly normal. The individual ganglion cells could be seen lying there without any change in them.

The next change that we noted was a rupture through the internal limiting membrane, which is a thin membrane that divides the retinal surface from the vitreous. We noticed that there was a break-through of the endothelio and glial proliferation through the internal limiting membrane. The new tissue coursed out over the surface of the retina and projected forward into the vitreous.

Subsequently this tissue increased markedly in its density and in its amount. The retina became elevated, and the tissue spread out over the surface of the retina, the loops of the elevated retina coalescing and forming a disorganized mass.

Even at this stage, one of the most characteristic pathological findings of early RLF is the apparent specific location of the disease process in the nerve fiber layer with extension inward toward the vitreous. Until fairly late in the develop-

ment, the outer portions of the retina appear perfectly normal. Of course, hemorrhage can supervene with subsequent organization. This causes a pushing forward of the lens and secondary glaucoma can develop.

I think that there are several things that we now know about RLF. First of all, there is a definite clinical entity which is distinct from any other type of disease that may produce an end picture of disorganization of the retina and vitreous; the disease is a disease of the retina, which occurs in premature infants. The clinical course of this disease is well understood and the pathology of the disease has now been illustrated from the very early initial lesion to the complete formation of the disorganized mass.

It is true that the term "retrolental fibroplasia" is a bad misnomer, because the disease is a retinal disease. The mass behind the lens, which is the most characteristic clinical finding in the late stages and from which the disease derived its name, is not the important part of the disease but is merely an accident. Many of the cases that develop the acute phases of RLF do not go on to form a retrolental mass. In some of them the disease subsides, leaving practically no perceptible evidence of the disease ever having been present. In other cases, the eyes may end up with simply a high degree of myopia. In others you may find as the end stage, simply pigmentation and scarring in the choroid and retina. In other cases in which the acute phase has been less severe, the disease may end with a distortion of the disc wherein all of the vessels at the disc will be twisted to one side, and the opposite side of the disc will have a heavily pigmented border. In still other cases you may find an end stage of the disease which resembles a retinal fold, which simply means that in one portion of the fundus you may find an area of detached retina covering over the scar tissue that extends from the disc toward a lesion in the periphery of the eye or to the posterior portion of the lens. And in still other cases you may get a partial membrane.

The end manifestations of the disease are varied and cover a multitude of clinical pictures. The presence of a large mass of tissue behind the lens is really an accident, but it is a most characteristic and most striking thing in the fully developed cases. It was for that reason that Terry used the name "retrolental fibroplasia".

In speaking about the incidence of RLF, you have to be very specific in defining what you mean. Do you mean the incidence of the acute phase of the disease, or do you mean the incidence of cases that show a significant disorganization of the globe? If you are speaking of the incidence of acute phase of the disease, which may go on to the formation of a complete membrane or to any variety of partial membranes or to very insignificant changes in the retina, in our experience this acute phase has occurred in approximately 50 per cent of all infants weighing less than 3 pounds. The incidence of the complete form of the disease is much less. Of course, there is a significant incidence for each of these various manifestations.

DR. INGALLS: What is the age of the youngest premature from which you have specimens?

DR. OWENS: About 4 to 6 weeks.

DR. INGALLS: Have you picked them up at such an early stage that only microscopic evidence was manifest? Can the condition occur before it can be detected by the ophthalmoscopic examination?

DR. OWENS: We know the condition can be seen with a microscope before we can see it with an ophthalmoscope. In one case in our series we had not observed anything clinically, but the infant showed the changes microscopically.

DR. WILLIAM A. SILVERMAN: Dr. Owens, what was the nature of these endothelial cells which had undergone proliferation?
DR. OWENS: They were apparently perfectly normal vascular endothelial cells which had undergone proliferation.

DR. JOHN C. LOCKE: Have you ever seen pathological specimens, particularly later ones, where the pathology does not seem to affect the ora serrata but seems to affect the posterior part of the retina?

DR. OWENS: Our pathologic specimens show most of the lesion in the zone immediately posterior to the ora serrata, not in the extreme periphery. Clinically we have seen cases that have had a preponderence of the lesion in the posterior pole. What caused endothelial proliferation without apparently any type of inflammatory reaction is very puzzling. We feel that the capillary proliferation is primary and the glial overgrowth around the budding capillaries is secondary. We have never found the glial proliferation in the absence of the capillaries, whereas we do have the capillary proliferation in the absence of the glial change.

DR. SAMUEL Z. LEVINE: Since this is a reversible process at any stage, is it conceivable that all premature babies under 3 pounds have this at birth and it has not been recognized? Are there routine histologic examinations of the eye of normal premature babies at birth?

DR. OWENS: As far as I know there has been no complete study of the histologic sections of the eyes of premature infants at birth. We have made some studies, and Dr. Reese, I know, has made some studies along these lines which have not been reported yet. My superficial answer to your question is that I don't believe all premature infants show these changes. Certainly that was Dr. Reese's feeling from an examination of, I think, 60 or 70 cases. We have not been able to find this disease present in all premature infants.

In all cases, even the severe ones, the active phase of the disease stops spontaneously, and the amount of damage that occurs depends upon the extent of involvement during the acute stage of the disease. We had one case that showed the acute phase of the disease and then subsided. That infant died, and we have the eye. In the retina, in the nerve fiber layer, you can see the scars of the disease. The active proliferation of the capillary endothelium has disappeared, but in the same characteristic whorl-like glomerular-like formation you can see the scars of the former proliferated endothelium, so that we do have a picture of what happens in the end stage of a disease which apparently had subsided.

DR. LOCKE: At the Institute we have specimens of eyes of 328 premature babies who died at or shortly after birth, and the thesis was previously held that perhaps there was some abnormal tissue in the periphery of the vitreous certainly has had to be abandoned.

We have, in some 15 per cent of these eyes, found inflammatory cells in the uvea, sometimes in quite large numbers. We do not know their significance.

Our findings in the cases showing RLF agree very well with the findings described by Dr. Owens. It would certainly seem that the basic pathologic lesion is a proliferation of capillary endothelial cells, and that everything else that occurs in the disease is a complication of their continued proliferation.

The first thing that we see clinically in many of our cases is neovascularization in the extreme periphery of the fundus. Tortuosity of the terminal portions of the vessels appears and becomes more marked. There is an increase in branching and in the number of vessels. Dilatation and tortuosity of the more proximal portions of the retinal vessels then follow. (Fig. 5). In cases where neovascularization in the periphery is the first finding, it seems easy to explain the secondary dilatation of the main vessels. If the capillary bed is increased, it seems only natural that the vessel feeding that capillary bed should dilate in order to look after the larger bed. However, there is another group of cases where the first clinical manifestation consists of dilatation and tortuosity of the more proximal portions of the vessels.

We have found clinically, in an occasional case, and pathologically in 2 cases, marked hyperemia of the iris; pathologically we have also observed dilation and increase in number of the vessels of the optic nerve. We have seen at least 1 case with a large hemangioma of the orbit.

I think you are all familiar with Dr. Reese's feeling that hemangioma of the skin may be related to RLF. It is difficult to get an exact statistical analysis of hemangioma of the skin. We have analyzed 378 cases of RLF that we have had the opportunity of observing and we have found that the incidence of hemangioma in these cases to be 18 per cent.

We are now contemplating a study of all premature babies which did not have RLF in an attempt to ascertain in our own hospital, where we feel we have good control of the records, what the incidence of hemangioma in premature babies without RLF is.

It is a question whether RLF is primarily a disease of the retina, or of the vitreous. My own opinion is that the question cannot be answered as yet. While it might appear to be a disease of the retina, it is however possible that the noxious agent is present in the vitreous and exerts from here its effect on the retinal capillaries, as suggested by Dr. Reese.

The first pathology occurs in the nerve fiber layer of the retina. Most of the changes seem to occur in the ophthalmoscopic periphery, but we have had sections of a globe in which the entire pathology is confined to the central part of the retina and there is no pathology at all in the peripheral portions of the retina.

(Dr. Locke has kindly supplied illustrative material from pathological specimens showing some of the changes encountered in RLF. (Figs 6, 7, and 8.)

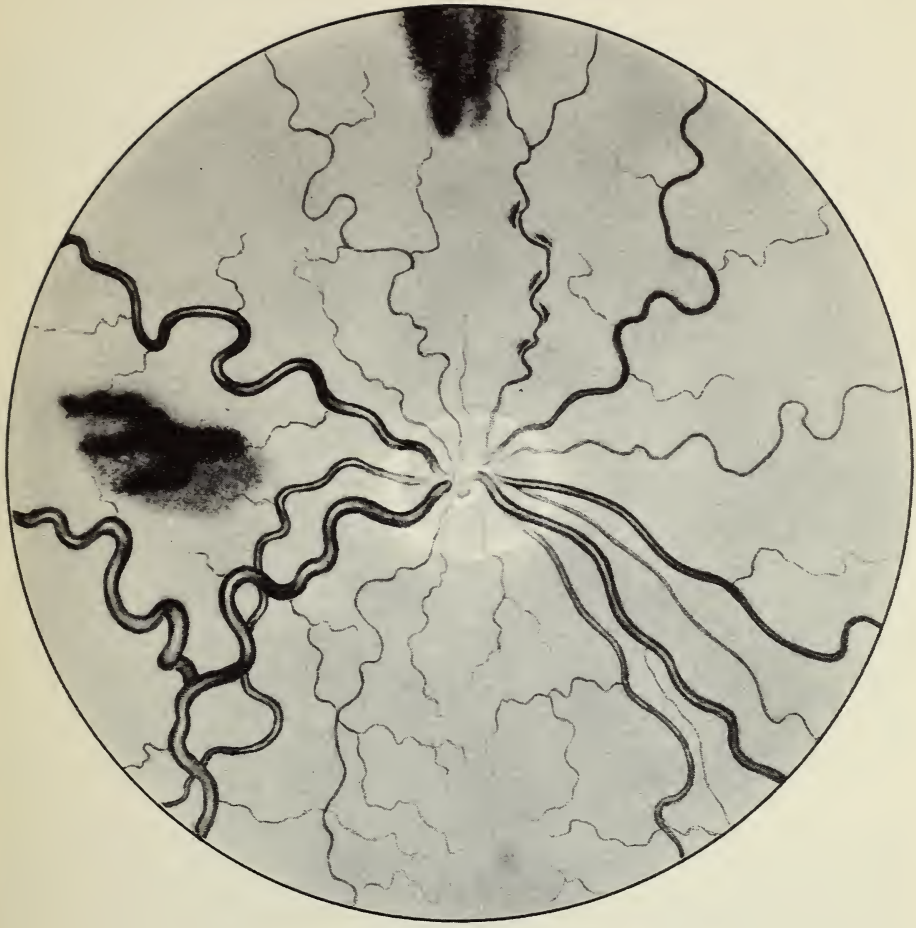

FIGURE 5

Early active retrolental fibroplasia showing dilatation and tortuosity of the retinal vessels and preretinal hemorrhages.

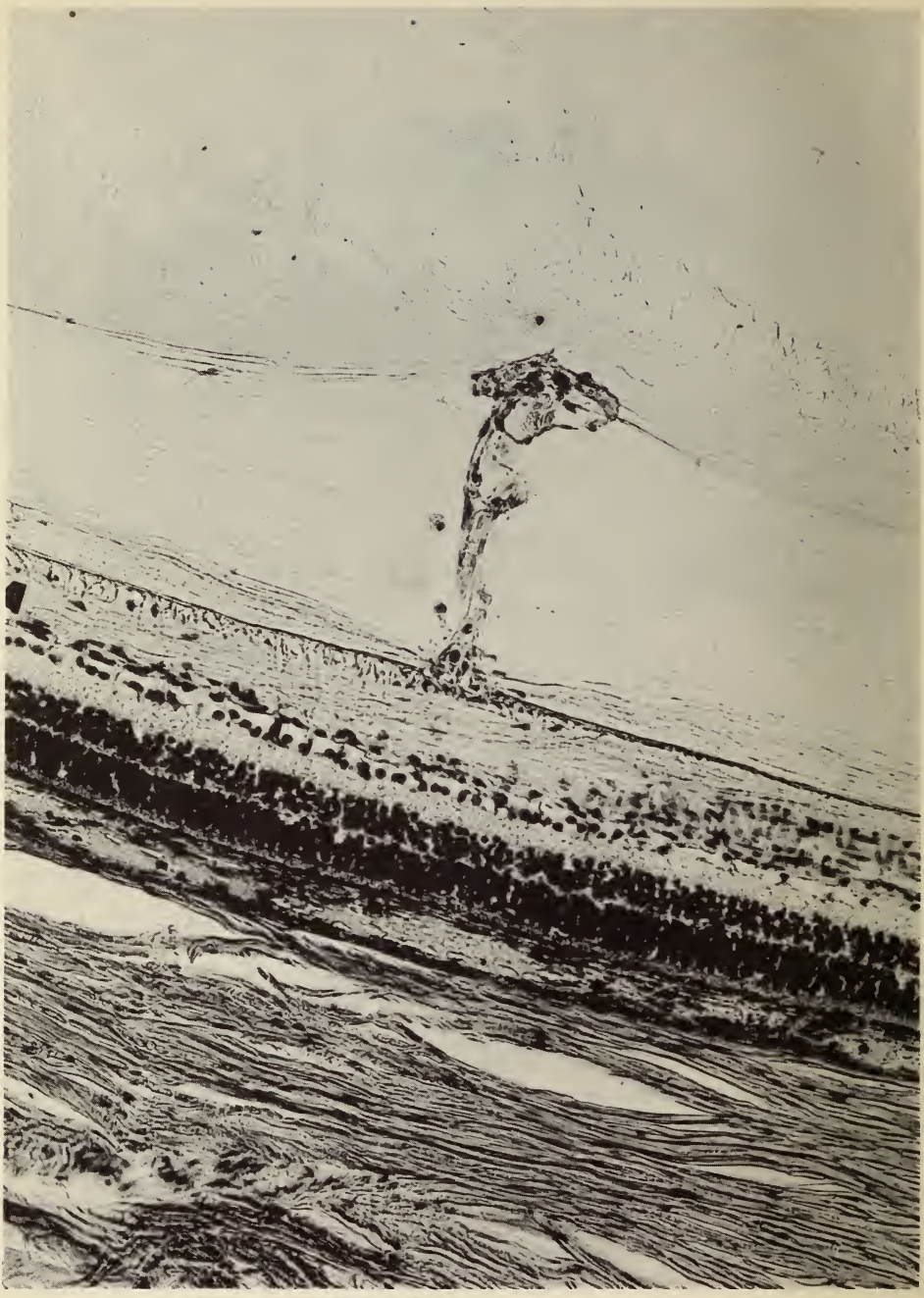

FIGURE 6

Photomicrographs to show early pathological changes in retrolental fibroplasia. These pictures show vascular budding into vitreous from the inner surface of the retina.

FIGURE 7

Photomicrograph showing pathology of early retrolental fibroplasia in an intermediate stage. This picture shows a large amount of angiomatous tissue on the surface of the retina which is being detached and drawn into folds. In this case is seen an associated hemangioma of the orbit.

FIGURE 8

Photomicrograph to show histopathology of a case of retrolental fibroplasia in an advanced stage. The fibro-angiomatous proliferation has brought about a complete detachment of the retina and these tissues together, form a dense membrane immediately behind the lens. Anterior and posterior synechiae are present.

DR. V. EVERETT KINSEY: With regard to this question of hemangioma, we made a study in 250 premature infants, and the incidence of hemangioma was within a percentage point identical for those infants who did develop RLF and those infants who did not. That was published back in 1949.

While I agree this was done in retrospect and some RLF may have been missed, I feel sure that there is not very much difference in the 2 groups.

DR. DAY: Among premature infants the smaller ones at birth have a higher incidence of RLF, do they not?

DR. OWENS: Yes. Comparable birth weights in any study that is being made on a comparison of babies is important. The disease is more common, at least in our experience, in babies of smaller birth weight.

That has not been exactly your experience in Boston, has it, Everett?

DR. KINSEY: No.

DR. SILVERMAN: We have found a statistically significant inverse correlation between birth weight and the age at clinical onset. The earliest onset occurred in an infant whose birth weight was 1845 grams. This infant was first examined at the age of 8 days, at which time the fundus abnormalities were well evident consisting of marked tortuosity of the retinal vessels, retinal hemorrhages, neovascularization, and retinal elevation.

A clinical onset after the age of 60-65 days has been very rare in our experience. In the few infants whose clinical onset of RLF was noted beyond the age of 65 days, the fundus changes underwent little or no progression.

We should like to predict from our birth weight/age at onset data that the earliest changes of RLF occurring in an infant of term weight will be detectable at or very close to birth.

DR. JOSEPH DANCIS: What mydriatic do you use?

DR. LOCKE: We use a drop of 2 per cent homatropine and follow in 2 or 3 minutes with a drop of 10 per cent neosynephrine.

DR. SYLVIA P. GRIFFITHS: How long after giving the mydriatic do you make your examination?

DR. LOCKE: Usually in 45 minutes or an hour an examination is made.

DR. DANCIS: Have you seen any adverse reactions from using 2 per cent homatropine?

DR. LOCKE: No, we have not. As a matter of fact, when the babies come to the follow-up clinic we give them 5 per cent homatropine.

DR. OWENS: We have used 2 per cent homatropine over a period of 6 years, and we have not seen any adverse reaction.

DR. DANCIS: We had one that I am pretty sure was a homatropine reaction following the use of 2 per cent solution.

DR. FRANKLIN P. BOUSQUET: We feel that the neosynephrine is more important for full dilatation.

DR. WILLIAM O. LAMOTTE, JR.: Our experience with several hundred infants has been satisfactory using 1 per cent homatropine and 2½ per cent neosynephrine given simultaneously and repeated at 5 minute intervals as indi-

cated. This provides full dilation and we have had no difficulty at all in seeing the periphery of the fundus.

DR. LOCKE: It has been stated by some that with the direct ophthalmoscope perhaps the periphery cannot be adequately viewed. I have examined some cases with a binocular indirect ophthalmoscope, the binocular factor giving depth, with the idea that retinal elevation could be picked up earlier. But I could not make the diagnosis any earlier with instrument. I find direct ophthalmoscopy very satisfactory myself.

DR. OWENS: We have used 2½ per cent neosynephrine with 2 per cent homatropine, and we get good dilatation.

DR. RAYMOND GRIFFITHS: Do you also use lid retractors?

DR. OWENS: No, we don't.

DR. KRAUSE: With a beginning lesion is it possible to have a spasm of arterioles before you have a venous dilatation?

DR. LOCKE: I have frequently noticed marked attenuation of the vessels in the retina, but this has occurred after we had commenced treatment with ACTH. I am not in a position to say whether it is part of the natural course of the disease or whether it is an effect of ACTH.

We have a baby who is now receiving ACTH and in whom the retinal vessels are so constructed we can hardly see them. Is it your experience that you do see this in the normal course of the disease?

DR. KRAUSE: That is right.

DR. OWENS: As to this question of the constriction of the arterioles, we have noticed occasionally constriction and attenuation of the arterioles in the fundus in premature infants, but we have not been able to correlate this constriction to an early phase of RLF. We see constriction occasionally, but in some of the infants there is no further progress. And in the babies that have developed RLF there may or may not be constriction or attenuation of the arterioles in the early stages.

I think Dr. La Motte has made similar observations. Is that right?

DR. LAMOTTE: Yes, although I have been somewhat impressed with the fact that perhaps 30 to 40 per cent of those who ultimately develop the vascular picture of RLF had marked constriction of the retinal arterioles.

DR. LOCKE: We have also seen the constriction that Dr. LaMotte mentioned before the baby developed RLF. I have always subscribed to the theory that it is usually seen in a very tiny or young baby and that the vessels have not developed to the normal size. Perhaps I have been wrong about that.

Does a picture such as that develop in unusually small babies or do you see that in a heavier weight baby?

DR. LAMOTTE: These were in babies between 3 and 4 pounds at birth. Incidentally, more than 50 per cent of our cases are in babies with that birth weight.

We have also been impressed with the birth weight of somewhere between 3 and 4 pounds as being a crucial time, even in these young infants weighing 2 pounds or under at birth. When they begin to get up to around 3 to 3½ pounds we think that is the time something is going to happen. And likewise, in our series, the babies which were around 3½ pounds at birth were those that seemed to have the most vicious and rapidly progressive type of disease.

DR. BOUSQUET: We have had a similar experience at the New York Hospital. Infants who had developed initial changes at about 1600 to 1800 grams seemed to progress faster and develop the disease sooner than infants who developed their initial changes at about 2000 grams in weight.

CHAIRMAN HOLT: Can we go on to Dr. Dancis' data on age incidence?

DR. JOSEPH DANCIS: This study was originally undertaken by Dr. Lewis, Dr. Guy and myself as a result of Dr. Kinsey's and Dr. Zacharias's paper about the possible relationship of vitamin A to RLF. In March, 1948, we changed the routine within the premature unit from the use of Drisdol and ascorbic acid to the use of a multivitamin preparation. (Fig. 9). We recalled infants born in our unit for 15 months prior to this change and compared the incidence in that group with the infants born in the unit after that date. Dr. Guy examined about 90 per cent of the infants included in this report, and saw all the infants on whom the diagnosis of RLF was made. This diagnosis of RLF was made only if changes were evident at the age of 6 months or older.

In figure 9 the incidence of RLF is graphed against time; the infants are divided into 3 weight groups. Each point represents the cumulative data of a 4 month period. The graph suggests a number of interesting features:

1. There is an inverse relation of birth weight to incidence.
2. The incidence of RLF in our unit is increasing. However, the increased incidence lagged behind the change in vitamin preparation, so that a relationship is unlikely.
3. Our incidence increased progressively during the period charted. An abrupt change in incidence would be more likely if the multi-vitamins had been the cause of the disease.
4. During the period charted we have made no known change in treatment, except in the vitamins, and in that we are using higher concentrations of oxygen, and doing weekly funduscopic examinations. Despite this we have progressed from a low incidence to a high incidence. This suggests, in a negative way, that factors such as the initial starvation period, the type of milk used, exposure to light, and treatment of anemia are not important factors in the etiology of RLF.
5. The last and most intriguing feature is the progressive involvement of the heavier weight groups. If we make the assumption that the heavier infants are less susceptible, then, the agent (or agents) that cause RLF has become more potent during our period of observation.

DR. CHARLES D. COOK: Do any of the cases reverse after 6 months?

DR. LOREN P. GUY: There may be a little improvement in the condition after 6 months, but I think you would still find some evidence.

DR. KINSEY: I should like to point out that we had this same transition very definitely in Boston. In 1942 we had 1 out of 90 cases in infants weighing more than 3 pounds, and in the next 5 year period, if I recall correctly, we had 40 out of about 120. All the figures were obtained by retroactive examination at the same time by the same individual. Bill, you have had the opposite experience in Baltimore, haven't you?

DR. OWENS: We have not noticed, over a 6 year period, any increased incidence in the babies over 3 pounds.

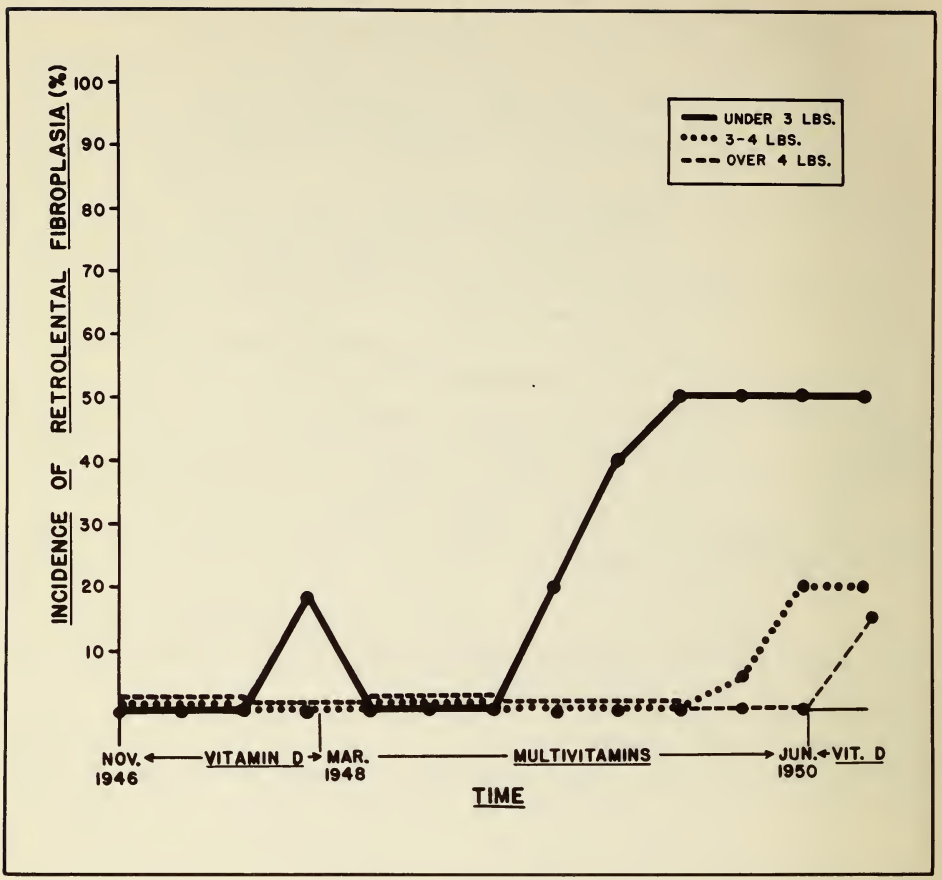
INCIDENCE OF RETROLENTAL FIBROPLASIA (%)
100
90
80
70
60
50
40
30
20
10
UNDER 3 LBS.
3-4 LBS.
OVER 4 LBS.
NOV. 1946
VITAMIN D
MAR. 1948
MULTIVITAMINS
JUN. 1950
VIT. D
TIME

FIGURE 9

DR. LEVINE: What has been the experience of New York Hospital?

DR. BOUSQUET: Our experience bears out the experience of Dr. Owens. In the 3 weight groups of under 1000 grams, 1000 to 1361 grams, and 1362 to 1650 grams there is progressively decreasing incidence of vessel changes, preretinal hemorrhage, vitreous hemorrhage, angiofibrous proliferation, retinal detachment and the final disease. (Fig. 10).

For example, our experience to date with 103 cases shows 78 per cent of cases with vessel changes in the less than 1000 grams weight group, 65 per cent in the 1000 to 1361 group, and 42 per cent in the large group. In our experience we found the disease to be remarkably similar, only showing a much faster course, to retinitis proliferans in the adult.

Duke-Elder and Doggert both say that 2 factors are operative in retinitis proliferans. One is the hemorrhage, and the 2nd one is inflammation, which apparently stimulates the hemorrhage to organize into fibrous tissue and eventually contract. In some of Dr. Reese's cases which he presented last fall there was evidence of round cell infiltration, and I wonder whether we are not dealing with 2 stimuli here, both circumscribed or both operating over a short period of time, which I think might be interesting from a therapeutic point of view.

DR. LAUPUS: I think Dr. Bousquet's chart indicates 1 other thing which he ought to bring out, and that is the high reversibility of the various stages of this condition. Even when retinal detachment was present in 27 infants, only 20 of them had residual disease; therefore, even where retinal detachment was present the retina could reverse to a normal state.

It is very difficult to draw conclusions from these data, because some of these infants have received ACTH as well with results that are not absolutely clear cut. But this reversibility is also seen in infants to whom ACTH was not given, so it is apparently a very real thing.

DR. OWENS: On that point, we observed, over a 2-year period, premature infants weighing less than 3 pounds that were receiving no type of treatment or therapy at all, and the figures that we have are strikingly similar to those presented by Dr. Laupus.

DR. UNSWORTH: Our data on incidence are presented in Table I. One point of interest is that we did not have any cases from December of 1949 until September of 1950, and during that time we gave up trying to treat them in any way. Nothing else was changed. I don't know why, but the incidence just dropped out entirely then.

Our incidence has a direct correlation with the birth weight. We don't need to consider the 5-6 pound group, because our incidence was zero in that group.

These are cases in which RLF developed permanent detectable changes and not those that were aborted.

Notice how close are these 2 years, 1948 and 1949; incidence then drops off in the year 1950, and so far this year we don't have any babies that are developing the disease.

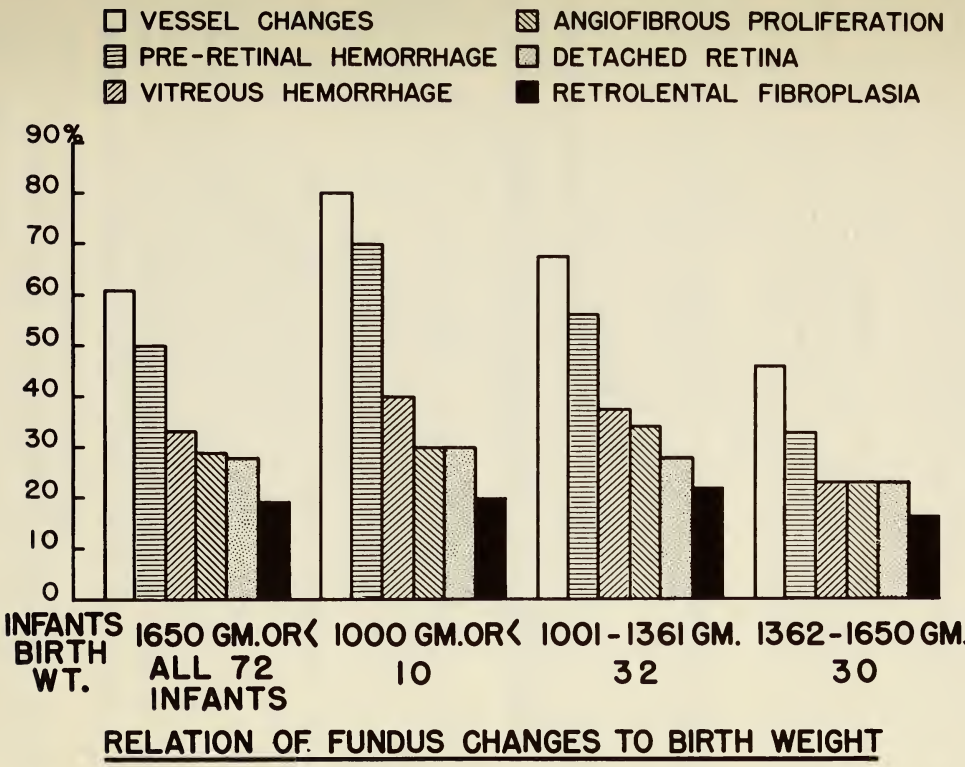
VESSEL CHANGES
ANGIOFIBROUS PROLIFERATION
PRE-RETINAL HEMORRHAGE
DETACHED RETINA
VITREOUS HEMORRHAGE
RETROLENTAL FIBROPLASIA
90%
80
70
60
50
40
30
20
10
0
INFANTS BIRTH WT.
1650 GM. OR < ALL 72 INFANTS
1000 GM. OR < 10
1001 - 1361 GM. 32
1362 - 1650 GM. 30
RELATION OF FUNDUS CHANGES TO BIRTH WEIGHT

FIGURE 10

TABLE I

NUMBER OF BABIES HAVING PERMANENT CHANGES OF RETROLENTAL FIBROPLASIA AT HARTFORD HOSPITAL

	1 to 3 lbs. Birth Weight			3 to 4 lbs. Birth Weight			4 to 5 lbs. Birth Weight			5 to 6 lbs. Birth Weight		
Year	Total No. Babies	No. with RLF	% of RLF	Total No. Babies	No. with RLF	% of RLF	Total No. Babies	No. with RLF	% of RLF	Total No. Babies	No. with RLF	% of RLF
1948	9	3	33.3	30	4	13.3	88	1	1.1	94	0	0
1949	9	3	33.3	35	4	11.4	106	2	1.9	111	0	0
1950	6	1	19.9	36	2	5.5	122	1	0.72	105	0	0
Total	24	7	29.1	101	10	9.9	316	4	1.2	310	0	0

CHAIRMAN HOLT: I wonder, Dr. Guy, if you would tell us about some of your early observations.

DR. GUY: I have examined a total of slightly under 300 premature infants here at Bellevue in the past several years. Among these I have seen 27 infants that had changes in the vitreous in the first 10 days of life. By "changes in the vitreous", I mean the vitreous was cloudy, ranging from a haze that obscured a clear view of the disk to a denser haze that obscured any details.

Along with this change in the vitreous, I found changes in the refractive index of the media. It appeared that the change in the refractive index occurred mainly in the vitreous, because usually the lenses were quite clear. The correction required varied from a minus 1 up to a minus 18, and that is extradordinary for such small eyes. The average correction was about 6 to 7 minus diopters. There must be a tremendous change in the refractive media.

Of the 27 infants who have been followed at least 6 months, 9 have developed an anatomical RLF, and 18 have not.

Two hundred forty-four cases had a clear media and a clear vitreous in the first 10 days of life. None of these have developed RLF, with 1 possible exception, a case that has some anatomical changes which may be the result of toxoplasmosis. We are trying to get that patient into the hospital for x-rays and further study.

If the observation is correct that infants show signs of RLF in the first 10 days of life, we may have to shift our emphasis on the disease back into the obstetrical period and the history of the mother.

DR. LOCKE: I have frequently noted cloudiness of the vitreous, particularly in the early weeks of life. And in some of our cases that have developed RLF, there was clouding of the vitreous. I have wondered whether this was part of the pathology and have rather suspected that it is. I have not gathered any positive statistics on the number of babies with apparent cloudiness of the media and the number of them that subsequently developed RLF.

DR. SILVERMAN: Did Dr. Guy mean to imply that this cloudiness of the vitreous was a temporary phenomenon and then cleared before the vascular changes were noted?

DR. GUY: Sometimes it is permanent, but some of them do clear. And apparently some of the cases that we have seen at 4 to 6 weeks of age, we have seen at an interval when the vitreous was clear, at which time we thought they were normal; then they went on and developed the disease.

DR. KINSEY: Do you think there is an excess of water in the region of the retina? Is there any edema at all?

DR. GUY: It is hard to study the retina through the cloudy media.

In the pathology of the retina, it is almost an axiom in ophthalmology that you never have a separation of the retina when the vitreous is healthy. So wouldn't you expect disease of the vitreous to precede separation of the retina? However, in a lot of these cases the vitreous clears up remarkably well prior to the separation of the retina or prior to the dilatation and constriction of the vessels.

DR. OWENS: On the point of myopia, we have many cases in whom the myopia will persist after the vitreous is completely clear.

Many babies in an acute phase of RLF develop a myopia; then, if you examine those babies even at 2 or 3 years of age, when the disease has completely subsided and the vitreous is perfectly clear, there is a very high degree of myopia in many of them. However, this could not be a change simply in the refractive index but is really an axial or curvature myopia.

There are probably 2 factors. One may be an index myopia, which Dr. Guy suggested, and the other we feel is axial or curvature myopia.

DR. DAY: How much axial myopia would take place using an 18 mm. lens?

DR. OWENS: It is about 6 or 7 mm.

DR. GUY: The myopia will vary from day to day. I determine it with an ophthalmoscope and do not think it is all in my nervous tension in focusing. It is too consistent, though it varies.

May I suggest that you who are fortunate enough to get eyes to study might measure the eyes before they are fixed, before any shrinkage takes place, and then you could settle the problem of myopia from an axial angle as well as an index angle.

DR. RALPH V. PLATOU: In the New Orleans area we see our fair share of cases of RLF, but it has amazed us that at Charity Hospital, where we deal entirely with an indigent group, in which the incidence of maternal disease, dietary privation, and inadequate prenatal care is extremely high, we have seen practically no cases of RLF. This, in our estimation, throws some doubt on a congenital basis for the lesion.

Remember that we do see some cases of RLF in the private hospitals and in consultations from outlying areas, among private patients. But, prior to June 1949, we had not recognized a single case in more than 3000 premature infants who have "graduated" from our Charity Hospital nurseries in recent years.

In a recent 2-year period there were 131 premature infants weighing less than 1500 grams who graduated from the unit. Of that 131, 80 were followed and carefully examined. Of 16 more we received reports from other physicians and parents that there was nothing wrong in the eyes. The adequacy of some of these examinations might be questioned, but at least we feel certain that none of these 16 had any gross ocular disease. Eight more died of unrelated causes of whom 5 came to autopsy with no evidence at that time of ocular disease. In 5 other infants, various ocular and ophthalmic lesions were found which were not related to RLF. This experience was reported by Exline and Harrington (J. Ped., 38:1, Jan., 1951).

The distribution of the maternal age corresponds to that which we have been able to discover from the reports which have appeared on RLF.

We could contribute nothing from our group except negative information. We were amazed at such a low incidence.

With regard to routine care of premature infants, our management differed in only 3 respects from those obtaining in many areas where the incidence

of RLF has been high. At present, we do not know or claim that any of these differences are important in relation to RLF.

The first difference is that we had leaned heavily toward "watering" our premature babies in the neonatal period. They are all given water at 12 hours, and we try to keep neonatal weight loss within 10 per cent of birth weight. This admittedly may be a practice born of ignorance, and despite our efforts we have had weight losses amounting to a good deal more than 10 per cent in some of the clinically edematous smaller premature infants. But most of our babies have had less than 10 per cent neonatal weight loss. The interval during which weight loss was maximal was in most cases less than 10 days.

The 2nd difference is that we use no breast milk whatsoever. The formulas that we use are of 3 types; a standard insocaloric evaporated milk and carbohydrate mixture, the Powers standard formula, and a high caloric condensed milk mixture.

The 3rd difference is that we had not used any water-soluble multi-vitamin preparation until more recently. We have given 100,000 units of vitamin D by intramuscular injection on the 1st day to all our prematures. We introduce oral vitamin D at 2, 3, or 4 weeks, when they are having no difficulty with their feedings. 50 mg of "C" is supplied in the daily formula.

In summary I should like to say that we do not have the foggiest notion of why we are blessed with a low incidence of this disease at Charity Hospital. The babies have been examined at weekly intervals for the early changes, but we have not done as frequent examinations as have been done in other centers. We don't intend to make any changes in our routine for the care of premature infants for the time being, however, because of our low incidence.

DR. DAY: How many actual cases have you had?

DR. PLATOU: In the last 9 months (since our report was completed,) we have had 4 cases; all of those weighed less than 1000 grams at birth. There is 1 additional case, a very questionable one. Dr. Allen believes it is a traumatic exudative retinitis with a good deal of preliminary hemorrhage. This baby was brought in to us at 4 days of age, weighing 1800 grams, and it had been horribly beaten in the process of delivery. We were amazed that this child had lived. He has a unilateral lesion which at this time (age 2 years) cannot be distinguished from the late stages of RLF.

DR. DAY: The 4 cases have all received the water-soluble multivitamin preparation?

DR. PLATOU: Three did, 1 didn't. That is the only variable that we are aware of, from our previous management.

I should say that the staff in charge of the premature infants has not been as vigorous in administering fluids since Dr. Clement Smith's contribution on prescribed dehydration for the premature, as we were during the period when these 131 small ones came through. I don't think that is important because, while we have not been as vigorous of late, we certainly have not gone all the way toward the regime of prescribed dehydration that Dr. Smith suggested.

DR. INGALLS: I should like to ask if your obstetrical practices are any different from anyone else's, particularly with respect to this large group of charity cases.

I have in mind the statistics which have come from Mary Cross's clinic, in Birmingham, England. She, like you, has had that very dramatic experience of finding such a low incidence and I believe there is not much reason to question her overlooking this condition. Her book indicates that a woman delivering markedly prematurely is allowed to have the baby with no anesthesia whatsoever, no, forceps, no nothing.

DR. PLATOU: We looked very carefully at that point, Dr. Ingalls, as far as all medication to the mother is concerned. Unfortunately, prenatal care in our clinics was received by less than 40 per cent of the total group, so we don't know what treatment the others received, if any. But in those that we have followed in our clinic, there appeared to be nothing at all remarkable about prenatal management.

As to delivery, our practice, perhaps as a result of our weekly obstetrical pediatric conferences, is to use only local anesthesia when a premature delivery is expected. But there is very very seldom any general anesthesia or analgesis given to the mother when a premature delivery is expected. The exceptions are usually for toxemic mothers.

DR. COOK: Did you imply that you felt there was much less RLF among the indigent group?

DR. PLATOU: No, I don't know that that necessarily obtains. Our hospital deals only with indigents, but the premature unit is one exception. We can accept, regardless of race, creed, or economic circumstances, a premature infant from anywhere in our state. I would say 95 per cent of our premature babies are from indigent families, however.

In the same 2 years in which we had no cases at Charity Hospital, with the largest population of prematures in the state, I saw 9 cases of RLF in infants born in private hospitals in the area of New Orleans. I don't think this is a geographic affair.

DR. GRIFFITHS: What proportion of the 131 cases whom you studied were Negro patients?

DR. PLATOU: Approximately 70 per cent.

DR. LEVINE: I was in Europe last fall, and went to France and Holland and Sweden. They had seen precisely 3 cases of RLF in Paris. While I was there a report came from Professor LeLong in which he described 3 or 4 additional cases. His explanation was that the small number of cases seen was probably due to lack of observation, lack of awareness.

The same situation existed in Holland. They had rarely seen a case of RLF until the condition was made known to them, and then they found 3 cases in 1 week. Then Professor E. Gorter, of Leyden, began following up the patients and found 3 or 4 others in serial examinations. But that did not exist in Sweden; in Sweden the ophthalmologists apparently examine the eye grounds of all premature babies practically from birth, and they had never seen a case of RLF. Their explanation is, in contrast to the experience of Dr. Platou, that all of their babies received breast milk, and most of our babies in the United States received cow's milk. That is true for the Dutch babies too; their babies receive breast milk.

So that factor perhaps might be eliminated, and one might concentrate on the multivitamins rather than on the breast milk.

DR. W. R. HEPNER, JR.: I should like to make a further remark on the Swedish experience. A friend of mine in Sweden tells me that all of the cases, which according to his memory total 5 as of March 1951, were not fed breast milk but were fed cow's milk.

CHAIRMAN HOLT: I think we might call a halt now and have a little refreshment in the next room.

(The conference recessed for luncheon at twelve thirty-five o'clock).

AFTERNOON SESSION

CHAIRMAN HOLT: We will now come to the questions of the etiology and the therapy of the disease. Perhaps Dr. Kinsey would like to start the ball rolling on the various concepts of the etiology.

DR. KINSEY: As most of you know, our studies have been centered in the Boston Lying-In Hospital; all the data that I am going to speak about comes from a study of this particular group of children. We have found from a study of 273 infants, about 80 of whom had RLF, that the age of the mother made no difference. That seemed to be a very definite finding, because the percentage of those mothers in the various decades of life who had children was identical within a percentage point.

With regard to the parity, primiparous women had an incidence of 9 per cent of children who had RLF. Those who had more than 1 child, we lumped into one group, and the incidence then was almost double. I suspect that the figures are large enough to be significant. What that means, I have no idea.

I would like to review some of the evidence that Dr. Zacharias and I obtained which indicated that the incidence of RLF might be dependent upon the amount of multiple vitamins in water-miscible form which were administered. The heavy line shown in the figure (Fig. 11) indicates the incidence of the disease in the premature infants having birth weights between 3 and 4 pounds. There is a striking increase in the incidence of the disease starting in the year 1942. We had observed only 1 case of RLF in 106 surviving prematures during 1938 to 1942 in this weight group, whereas there were 33 cases in 163 prematures during 1943-1947. The increase in the amount of water-miscible vitamins administered during the same period is shown by the dash-dot line in the figure. There is a good time correlation between the increase in the amount of vitamins and the incidence. While this positive correlation did not constitute proof of any causal relationship, it did suggest that the water-miscible vitamins should be withdrawn and the incidence again determined.

In 1948, the Vi-Penta was withdrawn from all the premature infants, and in its place vitamin D in a water-miscible menstruum, vitamins B and C in the usual dosage and iron were given. (You will note from Fig. 11, that we also obtained a positive correlation between the incidence and the amount of iron administered.) During the next year, 1949, vitamin A was omitted as before, vitamins D and C were given in a special water-miscible form provided by the U. S. Vitamin Corporation, but no vitamins B or iron were employed. It would have been desirable, of course, to omit all vitamins, but the pediatricians decided against omitting vitamins D and C.

The incidence of RLF in the 3-4 pound weight group during the 2 periods of study (1948 and 1949) were 18 and 15 per cent respectively . . . an insignificant change from the preceeding period. From these 2 experiments we conclude that RLF is not caused by the use of the water-miscible multiple vitamin preparation, thereby absolving Vi-Penta from any implications of being toxic or otherwise contributing to the disease.

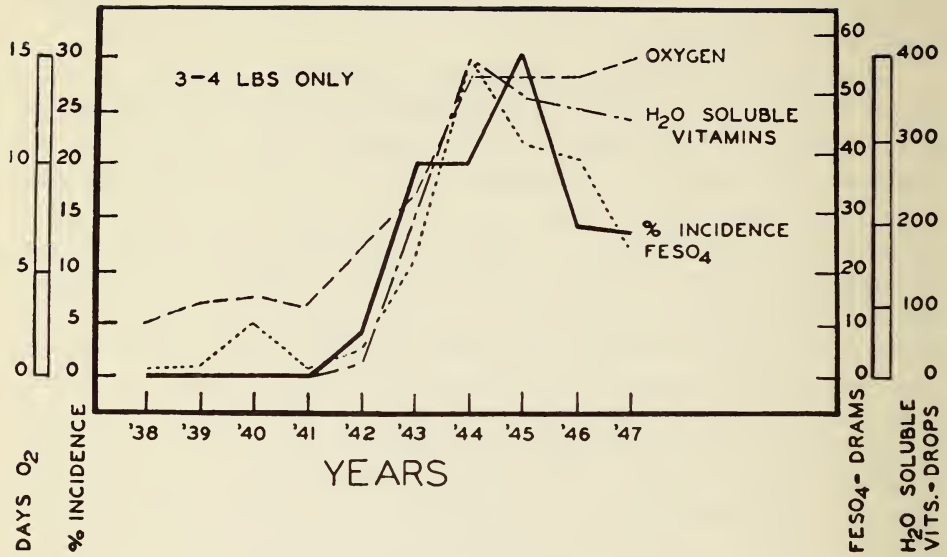

FIGURE 11

Correlation between the incidence of retrolental fibroplasia in premature infants born at the Boston Lying-in Hospital, and the administration of oxygen, ferrous sulfate (1 dram contains 1 grain, 65 mg. iron sulfate) and vitamin supplements given in a water-miscible form.

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We believe that the emulsifying or homogenating agents used in water-miscible vitamin preparations are without effect on the incidence of RLF because the incidence of the disease did not change during periods in which various homogenating and emulsifying agents were employed. (Dr. Krause agreed with this opinion although his group had once obtained some evidence suggesting that these agents might be toxic).

About the time this study was under way, Drs. William and Ella Owens presented evidence that vitamin E administered to premature infants could reduce the incidence of RLF. Dr. Julian Chisholm and I attempted to confirm these results. The experiments covered a period of 1 year and a half. Vitamin E was used in 2 ways, first as a therapeutic agent, and secondly, as a prophylactic agent. (Table II).

In order to demonstrate more clearly the possible influence of vitamin E therapeutically on the progression of RLF, the following classification was devised in which various stages of the disease are delineated:

NUMERICAL CLASSIFICATION OF STAGES IN THE DEVELOPMENT OF RETROLENTAL FIBROPLASIA

0. Normal
1. Enlarged arteries and veins — relatively straight.
2. Greater dilatation with tortuosity.
3. The changes of stage 2 plus generalized retinal edema, with some hemorrhage and/or vitreous haze.
4. The changes of stage 3 plus hemorrhage into vitreous and/or localized retinal detachment.
5. The changes of stage 4 plus disturbance in disc margins from retinal fold or partial peripheral or central membrane formation.
6. Partial to complete occlusion of pupil by membrane.

The administration of dl-alpha-tocopherol acetate therapeutically at the time the eyes had reached stage 2 of the above classification, failed in most cases to influence the rate of development of the disease. Vitamin E levels of the plasma were determined to make sure the dl-alpha-tocopherol acetate was absorbed.

During the period when dl-alpha-tocopherol was given therapeutically, the incidence was 11 per cent, or approximately half that of the previous year when dl-alpha-tocopherol acetate was not employed. This decrease in incidence is not significant.

Fifty-five infants received dl-alpha-tocopherol acetate prophylactically; 28 or approximately one-half, remained normal. The other half developed some acute manifestations of the disease. These figures are in agreement with those obtained by Dr. Owens in Baltimore.

In 3 infants the eyes reached stage 5 and, therefore, were presumably unaffected by the dl-alpha-tocopherol acetate. Nineteen reached stages 3 and 4; 17 of these eventually returned to normal and 2 had some residual change. Of those 22 infants who showed some initial changes, the eyes eventually returned to normal in 17, so that the percentage of regressions is high.

TABLE II

OUTCOME OF ACUTE MANIFESTATIONS OF RETROLENTAL FIBROPLASIA IN INFANTS GIVEN dl-ALPHA-TOCOPHEROL THERAPEUTICALLY OR PROPHYLACTICALLY

	No. of Infants	Stage of RLF						Incidence
		0-1	2	3-4		5-6		
Jan.-Sept. '49				Acute	Terminal	Acute	Terminal	
dl-alpha-tocopherol Therapeutically	46	25	13	3	1	5*	5	11% (5/46)
Sept. '49-July '50 dl-alpha-tocopherol Prophylactically	55**	28	9	19***	2	3****	3	5% (3/55)

*One infant (both eyes affected) of a pair of twins received no dl-alpha-tocopherol.

**The figure for the total number of infants (55) does not represent the sum of the four groups because in 4 infants the two eyes were classified differently.

***Two infants received blood transfusions and cortisone as well as dl-alpha-tocopherol.

****One infant received blood transfusion and ACTH as well as dl-alpha-tocopherol.

The incidence (stages 5 and 6) during the period in which the infants received dl-alpha-tocopherol acetate prophylactically was 5 per cent. While this incidence is the lowest which we had observed at the Boston Lying-in Hospital during the past 8 years, it is nevertheless difficult to decide whether the lowered incidence results from the use of dl-alpha-tocopherol acetate prophylactically.

Because of the extent of the fluctuations in incidence from year to year without apparent change in the regimen of the premature infant, statistical analysis is both difficult and of limited value in determining the effectiveness of the dl-alpha-tocopherol acetate.

I would hesitate to conclude that the dl-alpha-tocopherol acetate was of value although our results seemed to bear out those by the Baltimore group. I should be very much interested in the opinion of the audience as to whether the decreased incidence which we observed was a result of the use of dl-alpha-tocopherol.

My interpretation of the results is that we are dealing with a disease the incidence of which varies greatly from time to time and from place to place, and that thus far, none of the changes which we have made in the regimen of the premature infant has significantly altered the incidence.

CHAIRMAN HOLT: Dr. Owens, would you like to say anything about vitamin E at this point?

DR. OWENS: There are 3 things I should like to mention here. The 1st is that there is a tendency for this disease to spontaneously regress. One-half or slightly more of the babies who show the acute phase of the disease show spontaneous remission.

This makes the investigation of any type of therapeutic measure administered during the acute phase of the disease very difficult, because the chances are better than 1 in 2 that the infant to whom you have given any agent will show a spontaneous remission.

With this trouble confronting you, it seemed to us that the only way in which you can evaluate the effect of any agent is to have comparable statistics on a series of babies before the use of an agent, and a similar group of infants after the use of an agent.

We have given dl-alpha-tocopherol acetate in water-miscible solution beginning at the 7th day in 150 mg. doses to all infants in the nursery. In some babies we have raised that to 225 mg. a day if during the course of the therapy we thought there was a progression in the disease.

During the first 10 months of the study of the prophylactic use of vitamin E, we alternated cases, 1 group of infants receiving vitamin E prophylactically, and 1 group not receiving the vitamin E prophylactically. In the group that received the vitamin E, we eliminated vitamin A and iron. There was no vitamin B complex, and the patients received vitamins D, C, and K.

During that 10 month period, we noticed a drop from 22% to 4% in the final form of RLF with partial or complete retrolental membranes. At the end of that 10 month period, we were prevailed upon to shift all infants in our nursery

to vitamin E and to abandon the control series. Our experience now with vitamin E has extended over a period of 2½ years, approximately.

During this period we have found that the incidence of the early acute phase of retrolental fibroplasia was the same in the babies that received vitamin E prophylactically, and in those who had not received Vitamin E prophylactically in the previous period. That is, we found just as many cases with dilated blood vessels, and localized areas of graying in the fundus, and hemorrhages. But we did notice a change in the complete form of the disease. The incidence of complete retrolental membranes in our series dropped from 22 per cent in the group that had not received vitamin E prophylactically to 8 per cent in the group who had received vitamin E prophylactically. In comparison, the group in Boston found a drop of from 20 per cent before the use of vitamin E prophylactically to 5 per cent after the use of vitamin E prophylactically. So the effect of vitamin E, if any, would be in decreasing the amount of fibrosis and damage that has taken place during the acute phase of the disease, so that more eyes are salvaged.

It is perfectly possible that this drop which we have observed and which Dr. Kinsey has observed may be due to something entirely different from vitamin E administered in prophylactic manner. One of the things that would immediately come to mind would be the possibility of a spontaneous decrease in the incidence of the disease.

I was very much interested to learn this morning that in some of the other clinics, they have noticed during the recent years an actual increase in the number of cases that they were seeing; this does not mean that we do not have a spontaneous decrease in Baltimore and in Boston, but I think it would raise some doubt. Moreover, we have given this prophylactic vitamin E only to infants less than 3 pounds. In the group over 3 pounds, we have maintained the regimen that was present before 2½ years ago. The incidence of RLF in the group over 3 pounds has been consistently the same during the last 5 years. Since the 1st of January, 1951, we have gone back to alternate case studies with vitamin E.

Incidentally, there is no correlation between the initial blood level of vitamin E and the occurrence of the disease. The blood levels of vitamin E that our babies attained were much in excess of the normal adult serum level of tocopherol. The effect of vitamin E, if any, in reducing the severe forms of the disease, must be in a pharmacological action rather than as correcting a vitamin deficiency.

DR. LAMOTTE: I have some statistics in relation to vitamin E. These concern infants under 4 pounds at birth, and concern RLF in its final form, with infants blind or nearly blind in both eyes. The incidence at a single hospital in Wilmington, Delaware, has been unusually high in this birth weight group, and in the 2-year period from July, 1947, to July, 1949, was 32 per cent.

From July, 1949, to July, 1950, we inaugurated the use of dl-alpha-tocopherol in the same preparation and in the same dosage as used by Dr. Owens. Blood levels run for us by Dr. Kinsey in Boston, were considered adequate in every case, varying from 4 to 11 mg. per cent. During this year in which vitamin E was used, 19 babies under 4 pounds were studied. Seven of these developed the disease in its complete form, an incidence of about 36 per cent.

These figures involve low gross numbers and are not conclusive, but they indicate that the use of vitamin E prophylactically, begun from the 3rd to the 7th day of life, did not seem to alter significantly the incidence of the disease in that 1 year compared to the 2 previous years.

Since July, 1950, in the 10 months which have elapsed, we have not been using vitamin E prophylactically. Only 10 babies under 4 pounds have been available for study, in the last 10 months. Among these we had 1 case, an incidence of 10 per cent.

DR. KINSEY: Starting approximately in May, in the Boston group, in addition to giving vitamin E prophylactically, we gave a blood transfusion once a week using whole blood drawn fresh from mothers in their 3rd trimester of pregnancy. We went all out to supply anything that might possibly be needed. The blood was given at the rate of 5 cc. per pound, which the pediatricians assured us was the maximum blood transfusion that could be done with safety. We had 1 or 2 babies who, despite getting blood and despite getting the vitamin E, also got RLF. I think this was the greatest effort in giving blood transfusions, and I think one would be forced to conclude that there is no stray element present in whole blood which can be supplied in reasonably large quantities from the mother which specifically prevents RLF.

DR. LAUPUS: Beginning November 15, 1949, we began supplementing all infants with vitamin E as dl-alpha-tocopherol acetate, the same preparation, I believe, that Dr. Owens used. We initiated this with the 1st feedings and continued it until such a time that the infant had either complete, or arrested, RLF, or unequivocally normal eyes.

Rather than set up a control group on vitamin E, we set up a control group on vitamin A, because of evidence that had been presented by Dr. Kinsey in his article. Vitamin A, in the infants receiving it, consisted of 3,000 units given daily in an alcohol base, in combination with 1000 units of vitamin B. Those infants who were not given vitamin A were given Drisdol in a propylene glycol base.

At the present time, we can report on 98 of these infants, treated alternately. There were approximately the same number of infants in each weight group.

The incidence of early vascular changes in those receiving vitamin A was 63 per cent, and in those receiving no vitamin A, 65 per cent.

Eighteen per cent had residual changes in the vitamin A group compared with 14 per cent in the "no vitamin A" group.

The average level of vitamin E in the vitamin A group was approximately 4 mg. per cent, on a single spot determination at 5 to 6 weeks of age. The average level in the group not receiving vitamin A was somewhat higher, being approximately 6 mg. per cent. Interestingly enough, in the group with residuals, the levels were all in excess of 1 mg. per cent, which is considered a normal adult level for vitamin E. Insofar as the residuals are concerned, I do not believe that we can draw any conclusions from these figures, because of the small numbers involved, and also because we treated a number of these infants with ACTH as well.

CHAIRMAN HOLT: Dr. Ingalls, I hear you have some ideas on the etiology of RLF.

DR. INGALLS: I am quite impressed this morning with the way the genesis of the condition is being placed further and further back towards birth. When Terry first described RLF, it was pretty much a disease of 6 months old babies. Then the Owens by serial ophthalmoscopic examinations definitely showed an earlier onset—by 3 months of age. Next, microscopic studies showed changes at periods still closer to birth. Now that fascinating account by Dr. Guy may prove critically important, not only for early diagnosis and therapy, but as indicating genesis of the condition about the time of the premature birth.

What time transpires between birth and manifestations of the disease can just as well be regarded as an "incubation period", so to speak, as an interval during which the infant acquires the defect.

There is a very clear linkage of RLF with prematurity. Everyone is searching for something that we are doing to these premature babies after they are born. I submit that it is just as logical to give intensive consideration to the prenatal course, up to the moment that the baby emerges, with particular reference to the circumstances of placentation, oxygenation and delivery, and other events of pregnancy in those infants who get this condition.

I have been interested for 3 years now in studying anoxia as a teratogenic mechanism, just as Warkany has been interested in studying the role of dietary deficiency. The hypothesis tested is that anoxia is a teratogenic agent. This has been proven.

We have used pregnant mice putting them in a high-altitude chamber, at 2 altitudes, 25,000 feet and 27,000 feet. Each mouse goes in this chamber, on 1 occasion only, for 5 hours; and we have exposed mice in group of 10 on each of the possible days of pregnancy at each of these 2 altitudes. Whole litters are then screened for congenital deformities.

As a result of this kind of insult to the mothers, we find that we get all sort of dead and misshapen monstrosities, which correspond to abortions, still-births, and macerated fetuses. We also get wide spectrums of defects among survivors in a wide variety of organs and tissues—depending upon the stage of gestation at which mother and litter are insulted. The principle is of interest to the student of human disease. Who knows whether some babies die of whatever causes RLF? You have an index that they do in the high mortality among twin and triplet siblings of surviving babies who live to develop ocular anomalies. The dead siblings are worth studying intensively.

In mice, anoxia on the 8th day of gestation causes gross cerebral anomalies in about a 3rd of the litters. Fused ribs, spina bifida and hemivertebra are frequently observed. Other defects at subsequent periods of gestation are determined quite as much by the stage of embryonic development as by the degree of anoxic insult. On the 14th day of gestation, anoxia will produce cleft palate in about 30 per cent of the litters. The number with cleft palate within the litter has varied from 1 to 4.

With anoxia on the 16th day, we are finding so-called "open-eye" (Figure 12) in significant numbers. The mouse fetus normally has the eye closed at birth. This defect is similar to 1 of the deformities Warkany occasionally produced in

his vitamin-deficient animals. The anomalies produced by Warkany with riboflavin deficiency may ultimately prove to be related to anoxia. Members of the department of nutrition at the Harvard School of Public Health tell me that their animals suffering from riboflavin deficiency develop a polycythemia. Enzymatic systems are involved that relate to oxidation-reduction systems of the tissues. Moreover, the time relationship observed by Warkany appears to correspond to ours—for cleft palate at least. I am not aware that he timed the onset of "open eye". If he restored riboflavin to the mothers before the 14th day of gestation, however, he prevented cleft palate in the young.

I think it is of considerable interest and possibly pertinent to the problem of RLF, that we find the critical period for "open eye" just before birth. Pregnancy in the mouse lasts approximately 20 or 21 days. We deliver the litter by sections on about the 19th day so that the mother will not devour defective fetuses.

The work of Stockard here in New York about 1910 is still basic to the problem of teratogenesis of ocular defects and of contemporary interest because it also emphasizes the importance of tissue oxygenation. Stockard produced one-eyed cyclopian fish by growing the embryonating eggs in various antioxidants; chloretone, chloroform, lithium salts, alcohol, acetone, and ether.

CHAIRMAN HOLT: Dr. Parmer, would you like to comment on etiology?

DR. LEO G. PARMER: I don't know how many subscribe to the vitamin preparation theory of the etiology of RLF, but I hope to make this theory even more complex by presenting a bit of information about vitamin preparations.

Many of the drug and pharmaceutical products on the market change quite frequently because of advances in science. For example, 1 particular multivitamin preparation has had its formula changed innumerable times within the past 10 years. This particular product started off with an alcoholic vehicle which was then changed to propylene glycol and in recent years, following the trend, its solvent has been changed to that of an aqueous one.

Many investigators feel that the labels state the exact chemical composition of all products. However, that is not so. The Food and Drug Act requires a declaration of only the *active* ingredients for drugs. For foods or food supplements (and most vitamin preparations are classified as foods), all ingredients are to be declared, with some exceptions consistent with reason. An example of such an exception is the familiar declaration of "artificial flavors" instead of a listing of specific esters or aldehydes. There may be as many as 10 or more unlisted chemicals going into the production of a multi-vitamin preparation. For instance, the modern aqueous vitamin product contains solubilizing agents, anti-oxidants, chemicals to adjust the pH and the emulsifier, to which most of the attention has been paid as far as RLF is concerned. Then comes the list of better preservatives with the result that they are frequently changed. They may or may not add sweetening agents and finally flavoring agents. To add another variable to the problem, for the past 2 years, synthetic vitamin A has been substituted for natural vitamin A.

The above is an example of the number of chemicals that go into these preparations other than materials actually listed on the label. When an investigator wishes to analyze the effects of the Tweens, for example, in the problems of RLF,

FIGURE 12

Coronal section through head of a 19-day mouse embryo born with unilateral "open-eye". Low power view. The mother of this embryo was exposed to an atmosphere equivalent to 25,000 feet altitude an the 17th day of gestation.

The abnormal eye, on the right, shows the defective eyelid with partial collapse of the ophthalmic bulb, excessive folding both of the retina and sclera and outward displacement of the lens. Hemat. Eos.; magnification, x 50.

he must also take into consideration all the other chemicals which become variables in the experiment. The names of these are available, in many instances, through the cooperation of the pharmaceutical houses.

Nothing that I have said is to be construed as indicating any belief that vitamin preparations are or are not related to the problem of etiology of RLF.

CHAIRMAN HOLT: Very nice! Dr. Krause, would you like to say anything on the question of etiology?

DR. KRAUSE: The big question in the etiology is whether it is prenatal or postnatal. We have been entirely at a loss to explain our experience during this past year. Our incidence of RLF had very definitely increased year by year since 1937 until last year we observed the disease in 30-40% in our prematures. But we have had only 1 case in the past 12 months; as far as we know, there has been no change in treatment.

Of our total of about 60 cases, 10 have died, which is a large number. It appears that those cases that were born early (in 1937, 1938, and 1939) tended to die early. They died of intercurrent infection, and our highest death rate was in those years. Those that were born later (in the 1940's) did not tend to die.

Those children who got their fibroplasias late in life, who were term children, or heavy, tended to die. Since 1937 our group has been getting lighter. The disease has hit them later, and their survival has been much greater. The last ones are classified as normal mentally except for the loss of their eyesight, whereas in the early ones there was more microcephaly and more hydrocephaly.

At one time we changed our vitamin preparation and got a large drop in RLF. However, later on our incidence rose even a little higher than usual. Don't ask us why. We plotted them out by years, by evaluated conception, by location geographically, by occupation of the father and mother at the time, by the time of the pregnancy interval, the number of pregnancies, and all sorts of things like that, and we got nowhere.

We find that the incidence of fibroplasias in Illinois and the surrounding country is very spotty. For instance, in Iowa they had no fibroplasia arising from the University Hospital but they ran into 25 to 40 cases in the Eye Clinic.

You probably know that St. Louis has very few cases of RLF, but East St. Louis has lots. There are 3 hospitals there which the State of Illinois indicates are the proper places to bring prematures. So across the river they have lots of prematures, while St. Louis, with a much larger population just across the bridge, does not have them in the same ratio. That is an example of why statistics sometimes will lead you way off.

In Cook County Hospital, which is very large as you know—one of the largest hospitals in the United States—they run very low on RLF. During this past year, I believe they have had only 4. They made a special effort to have 1 ophthalmologist examine all the children.

CHAIRMAN HOLT: I wonder whether Dr. Levine would like to give us any ideas on the handicaps of the premature that might predispose to RLF.

DR. LEVINE: Up to 1940 we had never been able to save a baby whose birth weight was 1000 grams or less. After 1940 and up to the present time, we have had over 85 babies survive whose birth weight or whose neonatal weight in the 1st week of life was 1000 grams or less. We are now in the process of studying RLF in that group of 85.

My impression is that the incidence is no greater in that group than in the group between 1000 and 1500, but that is merely an impression at the present time.

I do not have any reason to implicate any of the handicaps that we know of with RLF.

DR. JANET B. HARDY: It is rather interesting that Dr. Harry Gordon had a similar wave of no cases for about 8 months, I think. He was in Baltimore about 3 or 4 months ago, and was very enthusiastic about the fact that they had had a rather high incidence up until that period, but then they had no cases in this 8-month period. He attributed it to a very careful use of oxygen and the fact they had been using oxygen tensions.

He went back to Denver, and I think there were 3 cases waiting for his arrival back in Denver. He wrote a letter very much chagrined but it points up the fact that apparently cases do occur in waves.

From our experience in Baltimore, I have only some very negative observations to make.

Dr. Park suggested to me some months ago that perhaps RLF might be related to the rate of growth of premature infants. He thought perhaps we were unwise to be putting a good deal of emphasis on making babies gain weight rapidly and forcing them to mature at a rate above which they did in years gone by.

Dr. Ella Owens picked out 3 groups of premature babies which we have studied rather extensively from that point of view. They were all small babies who were raised in the Harriett Lane Nursery during the same period of time and according to approximately the same routines.

A group of 15 small premature infants who presented no evidence of RLF gained an average of 22 grams per day of hospital stay.

Each infant in a 2nd group of premature infants was observed to have "partial" RLF, exhibiting some of the early changes of the disease but without going on to develop serious residual changes. These babies gained an average of 21.8 grams per hospital day.

The 3rd group of infants developed complete retrolental membranes. These infants gained an average of 22 grams per hospital day. Thus there is no significant difference between these 3 groups as far as rate of weight gain is concerned.

The records of all these babies were carefully analyzed to see if we could find any lead in the obstetrical history of the mother, or in the condition of the baby at birth, the kind of care the baby had received, particularly in relation to oxygen therapy. We could find essentially no difference between the three groups of infants. We could find no factors which might be responsible for the development of RLF.

Over the past 3 years a study of the incidence of rickets in premature babies maintained on various levels of vitamin D intake has been carried on in the Harriett Lane Premature Nursery. We have accumulated a great many serum calcium, phosphorus, and phosphatase determinations, all essentially normal. Neither the dosage of vitamin D nor the range of the blood chemical values studied seemed to bear any relationship to the incidence of RLF.

CHAIRMAN HOLT: Would anybody like to bring up other data bearing on the question of pathogenesis?

DR. LEVINE: I might mention that Dr. Baron from Paris, who studied with Dr. Reese and his group at Columbia, is convinced in his own mind that it is a virus disease, and he points out that the skipping from one institution to another would be consistent with the appearance of a virus in one community and not in another. He has suggested that the intraocular contents of infants with RLF be inoculated in egg embryo and other studies be made, and I think an attempt was made unsuccessfully on 1 occasion.

CHAIRMAN HOLT: I think Dr. Guy could mention a single case, too, in that connection.

DR. GUY: We took the aqueous from 1 youngster; Dr. Ward cultured it and found it negative for virus.

Maybe it is time for a laugh, so you can all laugh at me. After I heard Dr. Ingalls describe his altitude studies, I just wondered how many of the mothers had been up in airplanes.

DR. SILVERMAN: In the last case that entered Babies Hospital, interestingly the mother was an airline hostess. She said "I just tell you this because I flew all during my pregnancy."

DR. SYLVIA GRIFFITHS: At the Grace-New Haven Community Hospital we have surveyed the incidence of RLF for the 6-year period from January 1945 through December 1950. During this time we had 61 babies weighing 3½ pounds or less of which there were 11 cases, or 18%, of RLF with a more or less complete membrane occluding the pupil. In addition, there were 2 similar cases in the group above 3½ pounds. There was no significant yearly trend in incidence, but there was a direct correlation with birth weight, the disease occurring in the smallest infants. It was noted, however, that in 1945 and in 1949, in each of which years there were 4 cases of RLF, there was an overlapping of cases; in 1945 all 4 cases were in the premature nursery simultaneously, and in 1949 3 of the cases were concurrently hospitalized.

DR. INGALLS: I still think the role of uterine and systemic health of the mother has been underestimated in the causation of RLF. The basic concept of modern epidemiology is multiple causation. I do not see how the proposition can be avoided that prematurity itself is 1 of the causes. Even if vitamin deficiency or a toxin acting postnatally eventually is shown to play a contributory role in ocular disease of a prematurely born fetus, the placental and systemic disorders of the mother should still be scrutinized for the numerous causes of the predisposing prematurity.

In assembling their excellent statistics Kinsey and his coworkers correlated the incidence of numerous complications of pregnancy and labor among afflicted and unafflicted babies and found few significant differences. However, before their contributory role can be established or rejected—in terms of anoxia, for example—a far more intricate statistical problem must be solved for such variables as placental disease, hemorrhage, anemia, sedation, anaesthesia, presentation and duration of labor acting in variable combinations. Each may be expected to play a part in producing anoxia. Each influence may act as 1 of several triggers which have to be pulled before an explosion results.

CHAIRMAN HOLT: There are several aspects of therapy that we have not covered. I think everybody would like to hear more about ACTH and cortisone. I wonder whether Dr. Locke would lead off with the Columbia results.

DR. LOCKE: At the Presbyterian Hospital, Dr. Reese and Dr. Blodi in conjunction with Dr. Silverman and Dr. Day, began treating cases of RLF with ACTH in the spring of 1950. The results that we shall report on here will be all cases treated in 1950. In 1951 we have treated 14 cases and we have 6 controls, but I feel it is too early to report on this group of cases.

We are painfully aware of the great difficulty in evaluating any type of therapy in RLF. The ideal way, is to treat alternate cases. In RLF, however, if the agent that you are testing appears to be effective, it becomes most difficult to withhold the drug from a baby that is going blind.

Even if ACTH is found to influence the course of RLF favorably, there are some definite limitations to its use; 1st, with regard to the systemic hazards in its use: we have had 6 deaths out of 33 cases treated. I believe Dr. Silverman feels that ACTH might be partly responsible for the deaths, which were due to intercurrent infections of various types; the susceptibility of infants to infection appears to be increased. As a result of our experiences we have concluded that it is very unwise to give ACTH for a longer period than 3 weeks. Four of our total of 6 deaths occurred when the drug was given for a longer period than 3 weeks.

The 2nd limitation might be this: if the effect of ACTH takes place only while it is being given, and the drug can be given only for 3 weeks, since we know that the active part of the disease lasts longer than 3 weeks, there would be a certain period of time during which no therapeutic effect is acting.

Thirdly, if ACTH is effective, it seems to act mainly by preventing the disease from further progression. It cannot cause newly formed capillaries to disappear, and we cannot expect more of it than to arrest the disease at that stage at which therapy was commenced. Even in the successful cases the process does not always stop immediately, although many times it does. In the cases where we will report good results, it is not to be thought that ACTH has completely erased all the existing pathology present.

ACTH is of absolutely no value in the cicatricial phase of the disease. It has to be given early to be of value. There is no point in giving it to a baby over 3 months of age, nor when the active phase of the disease has reached the extent of almost entire retinal detachment. Many of the reports in the literature on the use of ACTH in RLF concern its use in the treatment of either the late active phase, or the cicatricial phase.

Our results are shown in Table 3.

We graded our cases into grades 1, 2, 3, 4, and 5. Grades 4 and 5 represent either complete or partial retrolental membranes, and constitute what we would call poor results. If half or more of the retina were involved, we would also call that a poor result. Another group with "congenital retinal folds" is classed neither as a success nor as a failure. Vision is often very seriously affected; on the other hand, the patient usually has sufficient vision to get around, and it is possible that it might have been much worse.

A good result with ACTH means that the permanent residual sequelae did not exceed that of a mass in the periphery of the fundus over a small sector.

Dr. Blodi and Dr. Reese and Dr. Silverman wanted to avoid treating those cases which were most likely to regress spontaneously. The cases that are analyzed here are only those cases which showed early progressive retinal edema or retinal elevation. We had 6 cases in 1950 which are not included in this table because they did not get past the blood vessel stage.

The age of onset of therapy has varied from 15 to 84 days, and therapy was usually commenced within 2 weeks of the diagnosis.

When evidence of the disease was found, the baby was watched 3 times a week. If retinal edema developed, and appeared to be progressing, therapy was instituted before the process got out of hand.

Our series includes cases from Babies Hospital and Lincoln Hospital. When we began treating the cases with ACTH, it was decided to use Lincoln Hospital cases as controls and the Babies Hospital cases for treatment. We no longer think that cases from another hospital constitute really effective controls.

We analyzed our results in terms of eyes rather than babies because sometimes a baby had a complete retinal detachment in 1 eye and a peripheral mass or retinal fold in the other eye. One eye had a good result and 1 eye a poor result. Out of 34 eyes (or 17 patients) 25 eyes ended with good results, 4 eyes were definite failures in treatment, and 5 eyes had results classified neither as success or failure —but "in between".

Of 14 eyes which we followed but did not treat, 4 regressed spontaneously, even though there appeared to be, at the beginning, progressive retinal edema and elevation, and 10 eyes went on to complete retrolental membranes.

I don't believe that these figures constitute a large enough series to be statistically analyzed.

I have analyzed the eyes in terms of the 2 different hospitals. Most of our control cases are from Lincoln Hospital, and we really don't have an effective series of controls from Babies Hospital.

Table 4 represents another method of analysis. The number of babies blinded by RLF during 1950 at Babies Hospital, is compared with the number of blind babies from Lincoln Hospital and (with the figures released by Dr. Bousquet and Dr. Laupus) from New York Hospital. New York Hospital had a total of 8 per cent of blind babies in the group under 1650 grams; Lincoln Hospital had a total of 11 per cent of blind babies in the group under 1760 grams; Babies Hospital, in

which almost all cases received treatment with ACTH, had an incidence of blindness of only 2.3 per cent. Not illustrated are Dr. Owens' figures for Johns Hopkins Hospital, with a total of 8 per cent of blind babies in the group under 1360 grams. I think our incidence of RLF is about the same as that at Lincoln, and is similar to that reported at Johns Hopkins by Dr. Owens. The question that we cannot answer yet is—is our lower incidence of blindness due to ACTH or to some other factor?

Starting a short while ago, we commenced treating by random selection, one group receiving glucosamine and the other ACTH.

TABLE 3

RESULTS OF TREATMENT OF ACTIVE RETROLENTAL FIBROPLASIA WITH ACTH IN 1950

An analysis of all cases showing vascular changes plus early progressive retinal elevation.

	NO. OF EYES	GOOD RESULTS	POOR RESULTS	IN BETWEEN
TREATED				
Babies Hospital	30	21	4	5
Lincoln Hospital	4	4	0	0
Total	34	25	4	5
UNTREATED				
Babies Hospital	4	2	2	0
Lincoln Hospital	10	2	8	0
Total	14	4	10	0

These figures can in no way be interpreted as demonstrating effectiveness of ACTH against RLF. The number of cases is too small and the controls inadequate. Further, comparative results of treated and untreated cases in 1951 are less encouraging.

TABLE 4

A COMPARISON OF THE NUMBERS OF BABIES MADE BLIND BY RETROLENTAL FIBROPLASIA AT DIFFERENT HOSPITALS IN 1950

Hospital	No. of Blind Babies	Total No. of Babies
Presbyterian	1.5 (2.3%)	65 (under 1500 gms)
Lincoln	7 (11.0%)	63 (under 1760 gms)
New York	6 (8.3%)	72 (under 1650 gms)

DR. SILVERMAN: Our selection of dosage of ACTH has been an empirical one. Our 1st infant treated with ACTH received 20 mgms. of the hormone per day (approximately 10 mgms. per kilo per day) a dose which we considered to be safe. At the time that treatment was begun progress of the fundus lesions had been determined by repeated ophthalmoscopic examinations over the preceeding 10 day period. The lesions were easily seen by all observers and consisted of marked tortuosity of the retinal vessels, dilatation of these vessels, hemorrhages, and peripheral retinal elevation. Within 48 hours after the onset of therapy, the eye lesions regressed almost to normal. There was some minimal dilatation and tortuosity; the hemorrhages and retinal elevation had disappeared.

We then reduced the dose by one-half because the infant had become very irritable. Progression of the fundus lesions followed this reduction of the dose of ACTH. The dose was increased to the initial level and continued to round out a total course of 14 days. The appearance of the retina slowly returned to an almost normal state, a small peripheral white mass remaining in each eye.

The dose of ACTH which we are using at the present time is 15 mgms. per kilo per day. This dose will cause a number of significant side effects, some of them terrifying, and certainly after a period of over 2½ weeks, I think quite dangerous. This dose also appears to be the minimal one which will elicit a maximal urinary output of formaldehydogenic steroids, will consistently inhibit the growth of the infant, and will cause marked irritability, ravenous appetite, transient edema and tachycardia. After prolonged treatment with ACTH, the infants who have not grown for 2½ weeks become quite debilitated. Many of them, especially recently, have developed intercurrent infections. The concurrent use of antibacterial therapy, with the administrations of ACTH in these premature infants, is mandatory.

Our policy differed for a short period of time. As Dr. Locke told you, the criterion originally offered for beginning ACTH was evidence of progression of the retinal lesions. We wondered whether it would be possible to improve the end appearance of the retina by starting therapy earlier, at the very first sign of disease. We realized that this would result in overtreatment, since a significant number could be expected to spontaneously regress. We have now had a short experience with this "early treatment" policy. We feel now that this policy is unwise because we have found it necessary to treat over a much longer period of time and have run into much more in the way of serious complications of therapy. Our present view is that if therapy is begun at the time of evidence of significant progression, approximately 2 weeks of treatment will be accompanied by either cessation of progress or regression of the eye lesions.

We have had occasion to give 2nd courses of ACTH to 7 infants. The interval between the 1st and 2nd course has varied from 36 hours to more than 2 weeks. The 2nd course of therapy has usually been associated with many more complications. Most of the deaths have occurred at the end of the 2nd course or at the end of a prolonged initial course of ACTH.

Urinary steroid outputs of the ACTH-treated infants have varied greatly on comparable doses per kilogram of body weight. There has been no correlation between a good output and a favorable outcome of RLF.

We have not had a sufficient experience with Cortisone. We have used it on 3 occasions following a course of ACTH. It is difficult to evaluate, certainly all of the side effects that are encountered with the use of ACTH can be predicted with Cortisone: growth inhibition, proneness to infection and in general the Cushing's syndrome.

CHAIRMAN HOLT: Dr. Bousquet, would you like to review briefly statistics at New York Hospital, or its experience?

DR. BOUSQUET: We have treated 13 infants with ACTH. Two of those received a course which we considered too short to be of any value, and they both developed severe retrolental membranes. The other 11 patients I have divided up more or less the way Dr. Locke did.

We treated 22 eyes. In 12 we found a good result, in 8 a poor result, and in 2 a complete failure.

This treatment was begun early, anywhere from 2 to 4 weeks after initial recognition of the lesion, in what Dr. Kinsey would call stage 2.

Usually these infants were treated with a dose of 25 mg. a day in 4 divided doses for a period of 10 days, and then 12.5 mg. a day in 4 divided doses for 2 to 4 days.

The infants who had the more severe preretinal hemorrhages and subsequent angiofibrous proliferation were the infants who eventually had a poor result or a complete failure. The 1 complete failure was an infant that was treated with 12.5 mg. in 4 divided doses for 14 days at the age of about 3 months and was thought to have complete arrest of the process. We followed this infant for 2 months subsequently in the clinic, and there was no progression of the disease. We thought it was completely arrested 2 months after treatment was ended. Four months later we were able to examine that infant again, and we found that he had developed complete retrolental membranes in both eyes. This must have occurred some 3 months after treatment, which we had thought had arrested the disease.

DR. LAUPUS: Although we gave all infants on ACTH prophylactic antibiotics (usually aureomycin), 3 infants developed upper respiratory infections. The 3rd was very seriously ill with what appeared to be a bronchiolitis of about 36 hours' duration.

We have tried to give the ACTH at a time when we thought the disease was no longer spontaneously reversible, so that these results represent treatment at a stage later, I think, than that at which Dr. Locke, Dr. Reese, and Dr. Silverman have treated.

CHAIRMAN HOLT: Dr. Cook, do you have some data from Boston?

DR. COOK: I have had experience with treating 6 cases at the Children's Hospital and 3 cases at Massachusetts General.

These cases were, I am afraid, poorly controlled. Only 5 were children in whom the disease was considered to be in the 2nd or 3rd stage and relatively reversible at the time the treatment was started. The others were treated in a quite late stage of the disease.

It has been our impression that treatment has stopped the disease process in 4 of these cases, and that in 3 out of these 4 cases the disease process has not progressed since the treatment was stopped.

In all of these cases we have used cortisone and not ACTH. The drug was usually administered intramuscularly, in the dosage from 40 to 60 mg. per day, using the higher dose initially for 6 or 8 days and then dropping down to around 40 mg. a day of cortisone intramuscularly.

We have had difficulty with lack of weight gain and debilitation, and in addition have seen diarrhea in 5 of the 9 cases. It has been persistent though not very severe. The diarrhea has been associated with a certain amount of dehydration, and in several of the infants there was severe shock and very high serum levels of sodium and chloride. In one child we found a serum sodium of 190 mEq. per liter and a chloride level of about 140 mEq. per liter, and in another case a serum sodium of 170 mEq. per liter and a comparable chloride level. Fortunately, all the children that have had diarrhea and dehydration and these very high serum levels have survived.

We have had 1 death, in a child receiving 150 mg. of cortisone a day orally — certainly a very large dose. The death was totally unexplained, and certainly was not associated with diarrhea, dehydration or high serum levels of electrolytes. This child had been on a dose of about 60 mg. of cortisone orally, which had then been gradually decreased and finally stopped. Then, due to the fact that the RLF seemed to be again progressing the treatment was reinstituted and the dose was increased finally up to 150 mg. per day.

We have routinely used antibiotics in association with the therapy, because of the fear of intercurrent infection. That fear has been transferred from our experience in nephrosis, where we have seen intercurrent infections hidden by the therapy quite frequently.

DR. DANCIS: Have you seen the same inhibition of growth observed with ACTH, Doctor?

DR. COOK: Yes, we have, although that again is hard to evaluate. There was the diarrhea, which contributed to a cessation of growth. Also, all of these children were on a low sodium formula. Whether or not this contributed to the lack of growth, I do not know.

CHAIRMAN HOLT: Dr. Lanman, would you like to say anything about your experience?

DR. J. T. LANMAN: We have treated with ACTH a total of 5 patients who were thought to be developing RLF. The ophthalmologic changes in these infants were noted between the 2nd and 13th day of life; the early diagnostic criteria in these cases were the vitreous haze and change in refractive index previously described by Dr. Guy. Subsequent changes followed the usual course of the disease. Treatment was begun between the 7th and 37th day, and then continued for from 30 to 56 days, with ACTH all drawn from a single Armour lot. The dose in these cases, usually ranged from 20 to 40 mg. per day, in 4 divided doses. The total dose received by any 1 patient ranged from 635 to 1850 mg., and this dose was sufficient to cause a rise, sometimes striking, in the formaldehydogenic steroid

output, a drop in eosinophils usually to zero, cutaneous pigmentation, usually some degree of edema from time to time, rounding of the face, and, in those instances in which we looked for it, hyperglycemia and glycosuria.

There was a striking increase in appetite. We have attempted to follow the appetite with increased calories and have observed that weight gain continues either at a subnormal rate or along the usual weight curves. The caloric intake may rise to 180 calories per kilo per day and in one instance even more.

Under this type of therapy, 4 of the 5 cases which we have treated have developed progressive changes of RLF, and now have the disease in a severe form. The 5th case is a patient in whom ophthalmologic changes were noted on the 2nd and 9th days of life, and treatment was begun on the 16th day. At that time there had already been a spontaneous regression of the disease, and the eye grounds were normal at the beginning of therapy. His eyes have been free of evidence of RLF since therapy.

DR. DAY: One possible explanation for the failure of ACTH to control the disease at Bellevue Hospital is the early institution of treatment there. Our results were good during 1950 when we administered ACTH only after progressing peripheral retinal detachment was observed. Our results were less good during the first part of 1951, when we tried ACTH as soon as vascular changes were noted. Under this treatment policy we had 2 failures, as well as 3 deaths, and in every case the courses of ACTH were prolonged, leading to debilitation. A policy of even earlier treatment, would therefore, on the basis of this experience, be expected to lead to poor results, and to prolonged periods of treatment, which are dangerous. It is certainly possible, though, that the cause of our good results in 1950 is not the use of ACTH but some unknown factor.

There is another possible cause for the discrepancy from the fact that in our series we are comparing untreated children at Lincoln Hospital and treated children at Babies Hospital. It is a matter of regret to us that we did not do an alternate case series in the same hospital. I should like to take this opportunity to make a plea to anyone trying to evaluate any single factor in this condition to use alternate cases or randomly selected cases in the same hospital during the same period of time.

DR. LANMAN: We are doing that; Dr. Mainland, who has been helping us with statistics, pointed out that with a disease in which the severity is changing, as it may be in this case, alternate selection of cases is not statistically as sound as a random number basis. If an upward sloping line represents increasing severity of the disease with time, strict alternation of cases will give two groups in which the average severity of the cases is not identical.

CHAIRMAN HOLT: Are there other people who have results on ACTH or cortisone to contribute?

DR. OWENS: We have had a limited experience with ACTH and cortisone. Our cases are divided into 2 groups. The 1st group consists of those cases that weighed over 1360 grams, who had received no alteration in their diet. In that group we have 2 cases that were treated at the stage of beginning retinal detachment, and in both of those cases the disease progressed to the formation of complete membranes.

In the other group, the group less than 1360 grams, we had 4 infants who had received either ACTH or cortisone in adequate dosages. In that group the ACTH or cortisone therapy was started when the disease was obviously progressing under the dietary regimen. And in those 4 cases the disease progressed to the formation of complete membranes. There has been a temporary halt in some cases, but the disease has gone on. With regard to dosage, none of the infants have received less than 25 mg. a day for a period of 3 weeks.

A possible explanation of our poor results with cortisone and ACTH is that the selection of the cases which were showing progression under vitamin E therapy might be a group having a more severe manifestation of the disease and therefore not responding as favorably to ACTH or cortisone as the other groups have experienced.

DR. DAY: Seven of our cases have shown great improvement in the eye subsequent to the giving of ACTH. The drug is then stopped, and then the disease begins again. Have you ever seen that during the natural history of the disease in a case not treated with ACTH?

DR. OWENS: Yes, we have seen 4 or 5 cases that were completely untreated and that had no dietary supplement at all, who have progressed and then subsided, and then 2 or 3 weeks later have shown further progression and the formation of complete membranes.

DR. LEVINE: All of the cases in Dr. Laupus' and Dr. Bousquet's study received vitamin E, so that the improvement that they observed with ACTH in their 11 or 12 patients was seen in those who had received vitamin E.

CHAIRMAN HOLT: Does anybody else have ACTH or cortisone cases that he would like to mention?

DR. UNSWORTH: We used ACTH in only 1 case. This case was 1 in which we had used chloromycetin 1st for a period of 2 weeks, and it continued to progress. We then gave it ACTH in addition, and it made absolutely no difference.

I might mention at this time that we tried chloromycetin on 4 cases, giving them 250 mg. 4 times a day. The first 3 cases, which had already begun to have retinal hemorrhages and progressive detachment, regressed within a few days after the chloromycetin was started. The 4th case progressed; it made no difference whatsoever there.

I am still not sure whether chloromycetin made any difference. One of the 3 cases to whom we gave it early showed regression and looked normal when sent home. It should have come to the follow-up clinic the following week, but, through a mistake on the part of the mother, did not come back for 3 weeks. At that time the baby had a retrolental membrane. On that child I again started chloromycetin, and it made absolutely no difference.

DR. OWENS: In our experience, approximately 60% of the cases showing the early manifestations of the disease will show no serious residual in the form of partial or complete retrolental membranes without any type of treatment.

The final half hour of the conference was spent in discussing the future course of investigation on RLF. The conferees agreed that information and studies along the following lines would be most helpful:

1. A compilation of geographical incidence of RLF. This data could perhaps best be collected by an organization such as The National Society for the Prevention of Blindness.
2. Standardization of the classification used to describe the disease according to clinical stages, for the sake of more meaningful reporting. Cooperation in this direction could be fostered by the preparation of a standard report form.
3. Group investigation of therapeutic procedures. This should be done with adequate controls and random case selection.
4. Further intensive investigation of the etiology and general pathological physiology of RLF. Here again the work should be done on a group basis.
5. A broad research program on the disease should be instituted with experimental animals. This could be very profitable if a proper experimental animal could be found.

In order to implement the above points, it was suggested that a committee be formed. This group could pool all case material and study all data submitted to it by groups willing to cooperate. After careful consideration the committee could then help coordinate the research program by serving as a clearing house for information. Furthermore, it could recommend, from a central office, treatment regimens for each participating group.

Chairman Holt appointed Dr. Kinsey as chairman and Dr. Foote as secretary of a temporary committee with powers to organize a permanent committee to handle the project. As a result, a permanent committee was organized at Atlantic City on June 13. This group is now actively engaged in following through on many of the recommendations outlined above.

SUMMARY

The present status of RLF and its therapy, as brought out in the Conference on Retrolental Fibroplasia held at Bellevue Hospital in New York City on April 28, 1951, may be summarized as follows:

1. *RLF is a definite clinical entity* which is distinct from any type of disease that may likewise produce an end picture of disorganization of the retina and vitreous. It is a disease primarily of the retina and vitreous which occurs almost exclusively in premature infants. There is some evidence that RLF may be part of a systemic disease, but further studies are needed to establish this point.

2. *Observations on the Clinical Course of the Disease* are in general agreement. The eyes are either normal at birth or show transient vitreous haze or opacities. Vascular dilatation and tortuosity appear about the 4th to 6th week of life followed by hemorrhages, exudate, retinal separation with formation of new blood vessels, and scarring which pulls the retina into a disorganized mass behind the lens. The disease progresses irregularly and may spontaneously regress at any time. The amount of residual damage depends on the extent of irreversible changes which have occurred when regression occurs. Many cases with early changes end with no demonstrable disease; from these there is a spectrum extending to complete retrolental scars with total loss of vision.

3. *The Etiologic Agent for RLF* is not known, nor is it known whether the disease results from prenatal or postnatal causes. Prenatal care and diet, prenatal disease, anesthetics and drugs during labor, postnatal administration of iron, oxygen and various vitamin preparations, the use of breast milk and various formulas for feeding of the premature infant, and numerous other factors have been explored without definite evidence that any are responsible. A few virus studies have been made without detecting an infectious agent.

4. *The Incidence of RLF* is not known for the country as a whole. The great increase in the number of cases observed since Terry's description of the first case in a premature infant in 1942 almost certainly reflects a rising incidence as well as closer examination of premature infants' eyes. Wide and unexplained variations in incidence occur in and between institutions and geographical areas from which reliable observations are available. The disease is found most commonly in the smaller premature infants of less than 3 pounds birth weight and only occasionally occurs in infants of more than 4 pounds at birth.

5. *No Effective Therapeutic Agent is Known.* Experience with ACTH and vitamin E have on the whole been discouraging in spite of limited claims to the contrary. The spontaneous resolution of the disease in a high percentage of affected infants makes evaluation of any therapeutic agent difficult.

6. In view of these findings, the conference proposed that a coordinated research program for the study of RLF be instituted. As a result, a permanent committee has been organized and is now engaged in implementing the various recommendations made at the conference.

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